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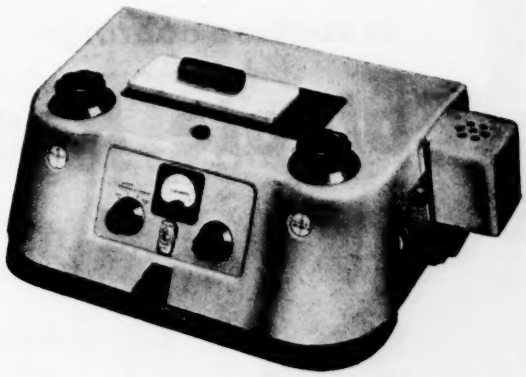

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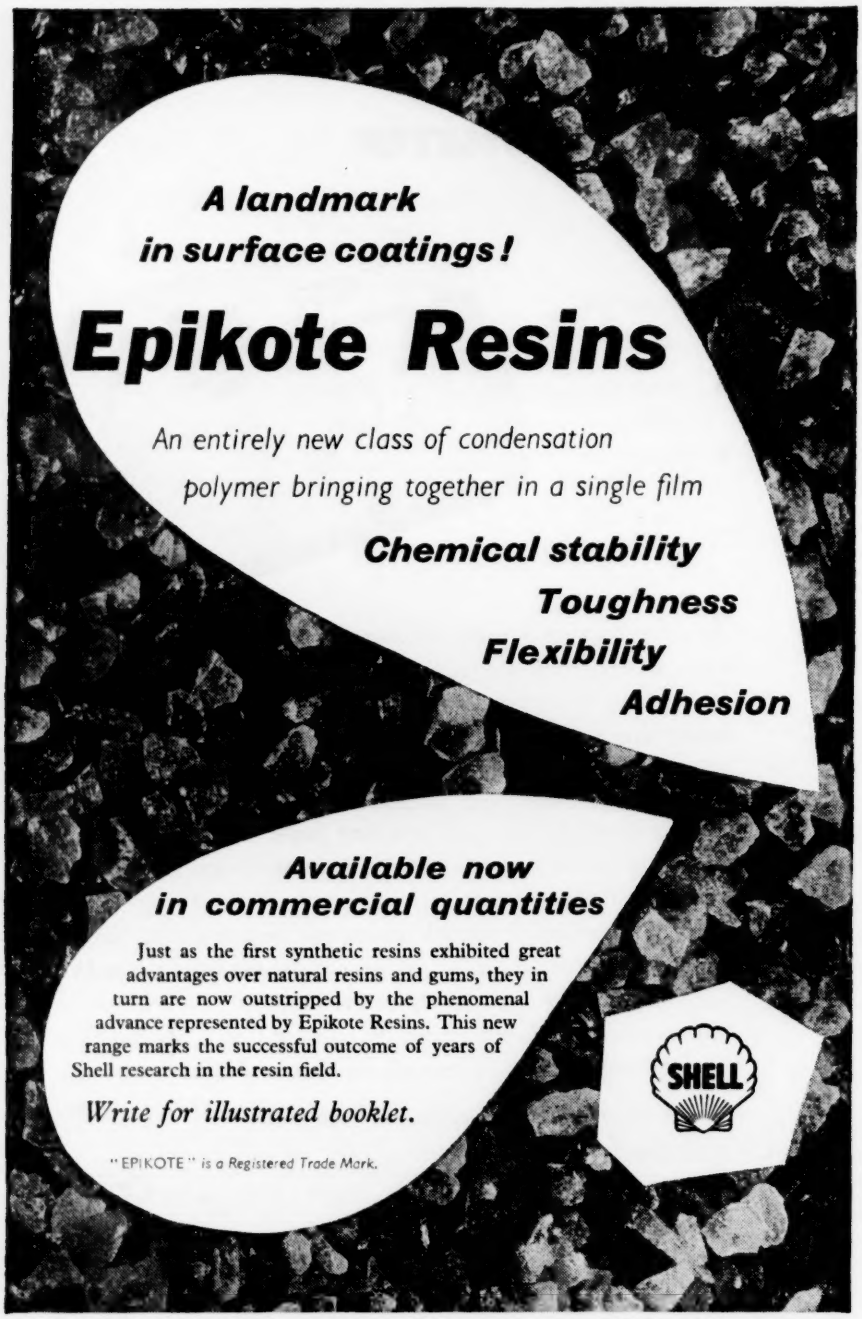
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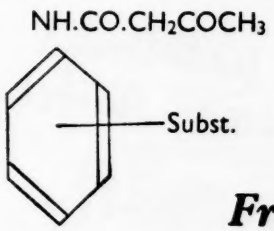

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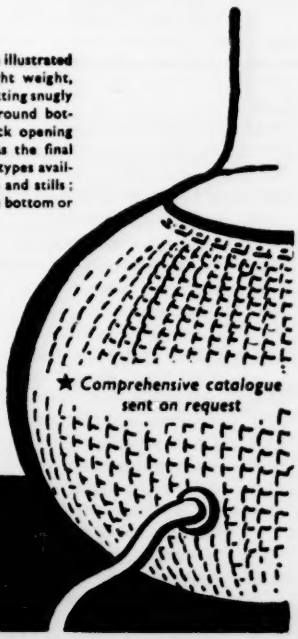

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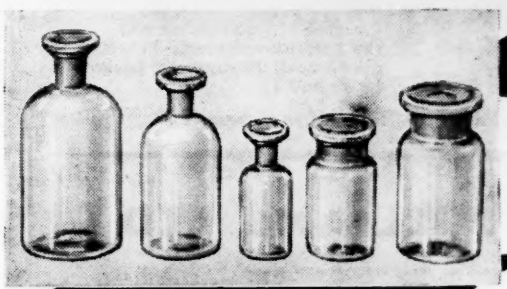

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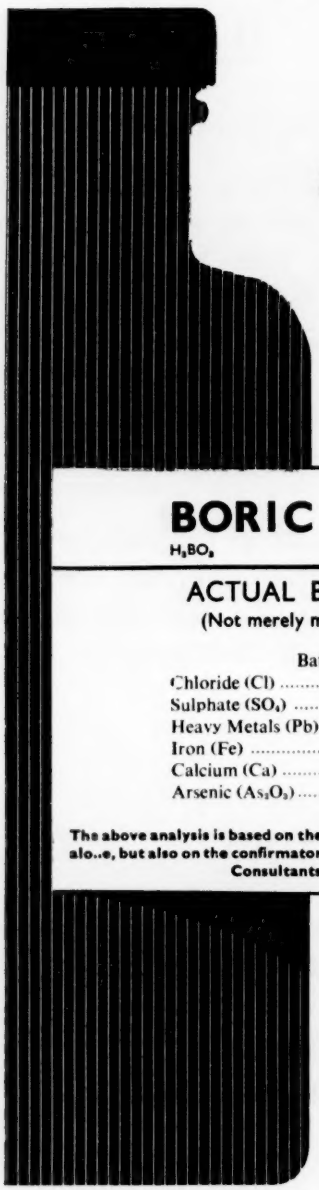

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Sulphate (SO_4)	0·0012%
Heavy Metals (Pb)	0·0001%
Iron (Fe)	0·0004%
Calcium (Ca)	0·0014%
Arsenic (As_2O_3)	absent

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CONTENTS.

PAPERS COMMUNICATED TO THE CHEMICAL SOCIETY.

General, Physical, and Inorganic.

PAGE

274. Substituted Benzidines and Related Compounds as Reagents in Analytical Chemistry. Part XII. Reagents for the Precipitation of Sulphate.
By R. BELCHER, A. J. NUTTEN, and W. I. STEPHEN. 1334

275. The Quantitative Analysis of Inorganic Compounds by Paper Chromatography.
By F. H. POLLARD, J. F. W. MCOMIE, H. M. STEVENS, and J. G. MADDOCK. . 1338

282. The Oxidation of Hydrazine in Aqueous Solution. Part I. The Nature of 1- and 2-Electron-transfer Reactions, with Particular Reference to the Oxidation of Hydrazine.
By W. C. E. HIGGINSON, D. SUTTON, and P. WRIGHT 1380

287. The Oxidation of Hydrazine in Aqueous Solution. Part II. The Use of ^{15}N as a Tracer in the Oxidation of Hydrazine.
By W. C. E. HIGGINSON and D. SUTTON. 1402

293. The Electrochemistry of Boron Trifluoride Co-ordination Compounds. Part VII. Degrees of Ionic Dissociation in the Molten State.
By N. N. GREENWOOD and R. L. MARTIN 1427

295. A Spectrophotometric Study of the Iron(III) Chloro-complexes.
By G. A. GAMLEN and D. O. JORDAN 1435

299. The Hydrothermal Chemistry of Silicates. Part III. Reactions of Analcite and Leucite.
By R. M. BARRER, L. HINDS, and E. A. WHITE 1466

304. Infusible White Precipitate: Some New Evidence as to its Structure, from a Study of its Thermal Decomposition.
By D. R. GLASSON and S. J. GREGG 1493

307. Studies in the Detoxication of Catalyst Poisons. Part IX. Dimethylphenylphosphine.
By E. B. MAXTED and G. T. BALL. 1509

316. Organometallic and Organometalloidal Fluorine Compounds. Part VI. Trifluoromethyl Arsenicals.
By H. J. EMELÉUS, R. N. HASZELDINE, and E. G. WALASCHEWSKI . . . 1552

317. Organometallic and Organometalloidal Fluorine Compounds. Part VII. Trifluoromethyl Compounds of Phosphorus.
By F. W. BENNETT, H. J. EMELÉUS, and R. N. HASZELDINE 1565

322. The Chromatography of Gases and Vapours. Part II.
By D. H. JAMES and C. S. G. PHILLIPS 1600

330. Hafnium Alkoxides.
By D. C. BRADLEY, R. C. MEHROTRA, and W. WARDLAW 1634

NOTES:

332. 1 : 3 : 7 : 8-Tetramethylxanthine.
By H. BADER and J. D. DOWNER 1641

333. Thermogravimetric Curves for the Decomposition of Octa-ammino-μ-amino-μ-nitrodicobaltic Sulphate and Dichlorobisethylenediaminocobaltic Hexachlorostibnate.
By D. GIBBONS 1641

Physical Organic.

271. Supposed Rotational Isomerism in the Succinic Acid Series.
By G. D. BUCKLEY 1325

273. Infra-red Spectroscopy and Structural Chemistry. Part V. Hydroxyphthalides.
By L. A. DUNCANSON, JOHN FREDERICK GROVE, and (MRS.) J. ZEALLEY . . 1331

276. Molecular-orbital Calculations for Clar's Hydrocarbon 1 : 13 : 12-6 : 16 : 7-Dibenzonaphthacene (Zethrene).
By C. A. COULSON and CARL M. MOSER 1341

PAGE

283. The Nitration of Guanidine in Sulphuric Acid. Part II. Kinetics of *N*-Nitration of the Guanidinium Ion and Denitration of Nitroguanidine.
By Gwyn Williams and R. J. J. Simkins 1386

288. The Hydrolysis of Acetic Anhydride. Part II. Catalysis by Pyridine.
By S. L. Bafna and V. Gold 1406

289. The Hydrolysis of Acetic Anhydride. Part III. The Catalytic Efficiency of a Series of Tertiary Amines.
By V. Gold and E. G. Jefferson. 1409

290. Quantitative Studies of the Reactivities of Mixed Carboxylic Anhydrides. Part IV. The Hydrolysis and Decomposition of Acetic Formic Anhydride.
By V. Gold and E. G. Jefferson 1416

296. The Effect of Solvents on the Tautomeric Equilibria of 4-Arylazo-1-naphthols and the *ortho*-Effect.
By A. Burawoy and A. R. Thompson 1443

300. The S_N Mechanism in Aromatic Compounds. Part IV.
By Joseph Miller and Vincent A. Williams 1475

302. Cyclic Meso-ionic Compounds. Part V. Further Studies on the Stereochemistry of the Sydnones, with a Description of a Heterodyne Capacitance Meter for Dielectric-constant Measurements in the Range 2—3.
By R. A. W. Hill and L. E. Sutton 1482

325. Lipoid–Water Partition Coefficients of Some Aromatic Bases.
By J. Cymerman-Craig and A. A. Diamantis. 1619

326. The Dipole Moments of Furan and Thiophen measured in the Dissolved and in the Gaseous State.
By B. Harris, R. J. W. Le Fèvre, and E. P. A. Sullivan 1622

327. The Dipole Moment of Pyrrole measured in the Dissolved and in the Gaseous State.
By A. D. Buckingham, B. Harris, and R. J. W. Le Fèvre 1626

Organic.

272. 1-Acetamidophenazine, 5 : 8 : 13 : 14-Tetra-azapentaphene, and 5 : 6 : 8 : 13 : 14-Penta-azapentaphene.
By Gerald H. Cookson 1328

277. Synthesis of Diaminoxanthones.
By A. A. Goldberg and H. A. Walker. 1348

278. Tuberculostatic Hydrazides and their Derivatives.
By Ng. Ph. Buu-Hoï, Ng. D. Xuong, Ng. H. Nam, Fernand Binon, and René Royer 1358

279. Epimeric Alcohols of the *cyclo*Hexane Series. Part IX. (±)-*cis*-3-Methyl*cyclo*hexylmethanol and (±)-*cis*-3-Methyl*cyclo*hexanecarboxylic Acid.
By L. H. Darling, A. Killen Macbeth, and J. A. Mills. 1364

280. ω-Halogenomethyl-pyridines, -quinolines, and -*iso*quinolines. Part IV. The Mechanism of Halogenation of Quinaldines.
By B. R. Brown, D. Ll. Hammick, B. H. Thewlis, and D. J. Walbridge. . 1369

281. Polyene Acids. Part VI. A New (*cis-trans*-)Isomer of Sorbic Acid and its Relation to Hexenolactones.
By Ulli Eisner, J. A. Elvidge, and R. P. Linstead 1372

284. 2 : 5-Dihydroxy-3 : 6-dimethoxyacetophenone and Its Degradation by Bromine.
By G. R. Ramage and C. V. Stead 1393

285. Synthesis of Analogues of Pyridoxine.
By (Mrs.) H. Davoll and F. B. Kipping 1395

286. αβ-Unsaturated Aldehydes and Related Compounds. Part III. The Addition of Alcohols to the Dimers of Acraldehyde and α-Methylacraldehyde.
By R. H. Hall 1398

291. Triterpenoids. Part XI. Some Stereospecific Reactions in the Lanostadienol (Lanosterol) Series.
By C. S. Barnes and D. H. R. Barton 1419

292. The Enzymic Synthesis and Degradation of Starch. Part XVIII. The Minimum Chain-length for Q-Enzyme Action.
By Stanley Peat, W. J. Whelan, and J. M. Bailey 1422

PAGE

294. The Oxidation of Monoethenoid Fatty Acids and Esters. The Preparation and Catalytic Oxidation of Highly Purified Brassidic Acid by Gaseous Oxygen.
By J. H. SKELLON and C. G. TAYLOR 1433

297. The Synthesis of Thyroxine and Related Substances. Part XIII. Some Further Analogues of Thyroxine.
By J. H. BARNES, R. C. COOKSON, G. T. DICKSON, J. ELKS, and V. D. POOLE . 1448

298. *iso*Quinoline Alkaloids. Part I. The Oxidation of Tetrahydropapaveroline.
By JOHN HARLEY-MASON 1465

301. Synthetic Plant Hormones. Part I. Some Esters of Phosphoric Acid.
By (MISS) M. H. MAGUIRE and G. SHAW 1479

303. The Chemotherapy of Tuberculosis. Part IV. Some *N*-Substituted Nicotinamides and Nicotinamidines.
By J. N. BAXTER and J. CYMERMAN-CRAIG 1490

305. Aminophenoxazines as Possible Antitubercular Agents. Part I. A New Method for the Synthesis of 3-Aminophenoxazine.
By B. BOOTHROYD and EDWARD R. CLARK 1499

306. Aminophenoxazines as Possible Antitubercular Agents. Part II.
By B. BOOTHROYD and EDWARD R. CLARK 1504

308. The Structure of Native Poly-D-glutamic Acid. Part IV. The Synthesis of Poly-L-glutamine and the Hofmann Degradation thereof.
By V. BRUCKNER, J. KOVÁCS, and K. KOVÁCS. 1512

309. Benz-1 : 3-oxathioles, Benz-1 : 4-oxathien, and αω-Bisarylthioalkanes.
By DOUGLAS GREENWOOD and HERBERT A. STEVENSON 1514

310. The Selective Absorption of Optical Antipodes by Proteins. Part II.
By WILLIAM BRADLEY and GERALD C. EASTY. 1519

311. Syntheses in the Morphine Series. Part IV. The Synthesis of *N*-Methylmorphinan.
By DAVID GINSBURG and RAPHAEL PAPPO 1524

312. The Synthesis of Sugars from Simpler Substances. Part VI. Enzymic Synthesis of D-Idoheptulose.
By P. A. J. GORIN and J. K. N. JONES 1537

313. Anodic Syntheses. Part VIII. New Syntheses of 3 : 13 : 19-Trimethyltricosanoic Acid.
By R. P. LINSTEAD, B. R. SHEPHARD, B. C. L. WEEDON, and (in part) J. C. LUNT 1538

314. Organic Peroxides. Part I. The Preparation of Alkyl Hydroperoxides from Hydrogen Peroxide.
By A. G. DAVIES, R. V. FOSTER, and A. M. WHITE 1541

315. The Reactions of Fluorocarbon Radicals. Part IX. Synthesis and Reactions of Pentafluoropropionic Acid.
By R. N. HASZELDINE and K. LEEDHAM. 1548

318. Studies in the Polyene Series. Part XLVI. The Synthesis of *o*-Tolyl and Mesityl Analogues of Vitamin A Acid.
By K. R. BHARUCHA and B. C. L. WEEDON 1571

319. Studies in the Polyene Series. Part XLVII. The Synthesis of Two Pentaene Esters related to Vitamin A.
By K. R. BHARUCHA and B. C. L. WEEDON 1578

320. Studies in the Polyene Series. Part XLVIII. The Preparation and Rearrangement of Some Dialkenylmethanols.
By K. R. BHARUCHA and B. C. L. WEEDON 1584

321. The Addition of Free Radicals to Unsaturated Systems. Part III. Chlorotrifluoroethylene.
By R. N. HASZELDINE and B. R. STEELE 1592

323. Coenzyme A. Part VIII. The Synthesis of Pantetheine 4′-Phosphate (*Acetobacter* Stimulatory Factor), a Degradation Product of the Coenzyme.
By J. BADDILEY and E. M. THAIN 1610

324. 3 : 4-, 3 : 5-, and 3 : 6-Dimethylcatechol.
By WILSON BAKER, H. F. BONDY, J. GUMB, and D. MILES 1615

328. The Chemistry of Reductone. Part III. Alkenediols related to Reductone.
By WESLEY COCKER, DAVID S. JENKINSON, and PETER SCHWARZ 1628

PAGE

329. The Hemicelluloses of Esparto Grass (*Stipa tenacissima*, L.). The Arabinose-rich Fraction.
By G. O. Aspinall, E. L. Hirst, R. W. Moody, and (the late) E. G. V. Percival 1631

331. 2-Thymyloxymethylglyoxalines and Related Compounds as Potential Antihistamines.
By H. Bader and J. D. Downer 1636

Notes :

334. *C*-Methylation of 4 : 6-Dihydroxycoumaran-3-one.
By T. P. C. Mulholland and G. Ward 1642

335. Some Pteridines related to Folid Acid. Part I. 2-Deamino-analogues.
By D. J. Brown 1644

336. Pyrimidine.
By Norman Whittaker 1646

337. Cumyl Phenyl Ether.
By A. M. Spivey 1647

338. Synthesis of 1-Alkyl-1 : 2 : 3 : 4-tetrahydro-2-3′-indolylmethyl-6 : 7-dimethoxy*iso*-quinolines and the Ready Cleavage of their Methiodides.
By J. M. Osbond 1648

Obituary Notice :

Sir Robert Waley Cohen 1651

INDEX OF AUTHORS' NAMES.

Aspinall, G. O., Hirst, E. L., Moody, R. W., and Percival, E. G. V., 1631.
Baddiley, J., and Thain, E. M., 1610.
Bader, H., and Downer, J. D., 1636, 1641.
Bafna, S. L., and Gold, V., 1406.
Bailey, J. M. See Peat, S., 1422.
Baker, W., Bondy, H. F., Gumb, J., and Miles, D., 1615.
Ball, G. T. See Maxted, E. B., 1509.
Barnes, C. S., and Barton, D. H. R., 1419.
Barnes, J. H., Cookson, R. C., Dickson, G. T., Elks, J., and Poole, V. D., 1448.
Barrer, R. M., Hinds, L., and White, E. A., 1466.
Barton, D. H. R. See Barnes, C. S., 1419.
Baxter, J. N., and Cymerman-Craig, J., 1490.
Belcher, R., Nutten, A. J., and Stephen, W. I., 1334.
Bennett, F. W., Emeléus, H. J., and Haszeldine, R. N., 1565.
Bharucha, K. R., and Weedon, B. C. L., 1571, 1578, 1584.
Binon, F. See Buu-Hoï, Ng. Ph, 1358.
Bondy, H. F. See Baker, W., 1615.
Boothroyd, B., and Clark, E. R., 1499, 1504.
Bradley, D. C., Mehrotra, R. C., and Wardlaw, W., 1634.
Bradley, W., and Easty, G. C., 1519.
Brown, B. R., Hammick, D. Ll., Thewlis, B. H., and Walbridge, D. J., 1369.
Brown, D. J., 1644.
Bruckner, V., Kovács, J., and Kovács, K., 1512.
Buckingham, A. D., Harris, B., and Le Fèvre, R. J. W., 1626.
Buckley, G. D., 1325.
Burawoy, A., and Thompson, A. R., 1443.
Buu-Hoï, Ng. Ph., Xuong, Ng. D., Nam, Ng. H., Binon, F., and Royer, R., 1358.
Clark, E. R. See Boothroyd, B., 1499, 1504.
Cocker, W., Jenkinson, D. S., and Schwarz, P., 1628.
Cookson, G. H., 1328.
Cookson, R. C. See Barnes, J. H., 1448.
Coulson, C. A., and Moser, C. M., 1341.
Cymerman-Craig, J., and Diamantis, A. A., 1619.
Cymerman-Craig, J. See also Baxter, J. N., 1490.
Darling, L. H., Macbeth, A. K., and Mills, J. A., 1364.
Davies, A. G., Foster, R. V., and White, A. M., 1541.
Davoll, H., and Kipping, F. B., 1395.
Diamantis, A. A. See Cymerman-Craig, J., 1619.
Dickson, G. T. See Barnes, J. H., 1448.
Downer, J. D. See Bader, H., 1636, 1641.
Duncanson, L. A., Grove, John Frederick, and Zealley, J., 1331.
Easty, G. C. See Bradley, W., 1519.
Elks, J. See Barnes, J. H., 1448.
Eisner, U., Elvidge, J. A., and Linstead, R. P., 1372.
Elvidge, J. A. See Eisner, U., 1372.
Emeléus, H. J., Haszeldine, R. N., and Walaschewski, E. G., 1552.
Emeléus, H. J. See also Bennett, F. W., 1565.
Foster, R. V. See Davies, A. G., 1541.
Gamlen, G. A., and Jordan, D. O., 1435.
Gibbons, D., 1641.
Ginsburg, D., and Pappo, R., 1524.
Glasson, D. R., and Gregg, S. J., 1493.
Gold, V., and Jefferson, E. G., 1409, 1416.
Gold, V. See also Bafna, S. L., 1406.
Goldberg, A. A., and Walker, H. A., 1348.
Gorin, P. A. J., and Jones, J. K. N., 1537.
Gregg, S. J. See Glasson, D. R., 1493.
Greenwood, D., and Stevenson, H. A., 1514.
Greenwood, N. N., and Martin, R. L., 1427.
Grove, John Frederick. See Duncanson, L. A., 1331.
Gumb, J. See Baker, W., 1615.
Hall, R. H., 1398.
Hammick, D. Ll. See Brown, B. R., 1369.
Harley-Mason, J., 1465.

Harris, B., Le Fèvre, R. J. W., and Sullivan, E. P. A., **1622**.
Harris, B. See also Buckingham, A. D., **1626**.
Haszeldine, R. N., and Leedham, K., **1548**.
Haszeldine, R. N., and Steele, B. R., **1592**.
Haszeldine, R. N. See also Bennett, F. W., **1565**, and Emeléus, H. J., **1552**.
Higginson, W. C. E., and Sutton, D., **1402**.
Higginson, W. C. E., Sutton, D., and Wright, P., **1380**.
Hill, R. A. W., and Sutton, L. E., **1482**.
Hinds, L. See Barrer, R. M., **1466**.
Hirst, E. L. See Aspinall, G. O., **1631**.
James, D. H., and Phillips, C. S. G., **1600**.
Jefferson, E. G. See Gold, V., **1409**, **1416**.
Jenkinson, D. S. See Cocker, W., **1628**.
Jones, J. K. N. See Gorin, P. A. J., **1537**.
Jordan, D. O. See Gamlen, G. A., **1435**.
Kipping, F. B. See Davoll, H., **1395**.
Kovács, K. See Bruckner, V., **1512**.
Kovács, J. See Bruckner, V., **1512**.
Leedham, K. See Haszeldine, R. N., **1548**.
Le Fèvre, R. J. W. See Buckingham, A. D., **1626**, and Harris, B., **1622**.
Linstead, R. P., Shephard, B. R., Weedon, B. C. L., and Lunt, J. C., **1538**.
Linstead, R. P. See also Eisner, U., **1372**.
Lunt, J. C. See Linstead, R. P., **1538**.
Macbeth, A. K. See Darling, L. H., **1364**.
McOmie, J. F. W. See Pollard, F. H., **1338**.
Maddock, J. G. See Pollard, F. H., **1338**.
Maguire, M. H., and Shaw, G., **1479**.
Martin, R. L. See Greenwood, N. N., **1427**.
Maxted, E. B., and Ball, G. T., **1509**.
Mehrotra, R. C. See Bradley, D. C., **1634**.
Miles, D. See Baker, W., **1615**.
Miller, J., and Williams, V. A., **1475**.
Mills, J. A. See Darling, L. H., **1364**.
Moody, R. W. See Aspinall, G. O., **1631**.
Moser, C. M. See Coulson, C. A., **1341**.
Mulholland, T. P. C., and Ward, G., **1642**.
Nam, Ng. H. See Buu-Hoï, Ng. Ph., **1358**.
Nutten, A. J., See Belcher, R., **1334**.
Osbond, J. M., **1648**.
Pappo, R. See Ginsburg, D., **1524**.
Peat, S., Whelan, W. J., and Bailey, J. M., **1422**.
Percival, E. G. V. See Aspinall, G. O., **1631**.
Phillips, C. S. G. See James, D. H., **1600**.
Pollard, F. H., McOmie, J. F. W., Stevens, H. M., and Maddock, J. G., **1338**.
Poole, V. D. See Barnes, J. H., **1488**.
Ramage, G. R., and Stead, C. V., **1393**.
Royer, R. See Buu-Hoï, Ng. Ph., **1358**.
Schwarz, P. See Cocker, W., **1628**.
Shaw, G. See Maguire, M. H., **1479**.
Shephard, B. R. See Linstead, R. P., **1538**.
Simkins, R. J. J. See Williams, G., **1386**.
Skellon, J. H., and Taylor, C. G., **1433**.
Spivey, A. M., **1647**.
Stead, C. V. See Ramage, G. R., **1393**.
Steele, B. R. See Haszeldine, R. N., **1592**.
Stephen, W. I. See Belcher, R., **1334**.
Stevens, H. M. See Pollard, F. H., **1338**.
Stevenson, H. A. See Greenwood, D., **1514**.
Sullivan, E. P. A. See Harris, B., **1622**.
Sutton, D. See Higginson, W. C. E., **1380**, **1402**.
Sutton, L. E. See Hill, R. A. W., **1482**.
Taylor, C. G. See Skellon, J. H., **1433**.
Thain, E. M. See Baddiley, J., **1610**.
Thewlis, B. H. See Brown, B. R., **1369**.
Thompson, A. R. See Burawoy, A., **1443**.
Walaschewski, E. G. See Emeléus, H. J., **1552**.
Walbridge, D. J. See Brown, B. R., **1369**.
Walker, H. A. See Goldberg, A. A., **1348**.
Ward, G. See Mulholland, T. P. C., **1642**.
Wardlaw, W. See Bradley, D. C., **1634**.
Weedon, B. C. L. See Bharucha, K. R., **1571**, **1578**, **1584**, and Linstead, R. P., **1538**.
Whelan, W. J. See Peat, S., **1422**.
White, A. M. See Davies, A. G., **1541**.
White, E. A. See Barrer, R. M., **1466**.
Whittaker, N., **1646**.
Williams, G., and Simkins, R. J. J., **1386**.
Williams, V. A. See Miller, J., **1475**.
Wright, P. See Higginson, W. C. E., **1380**.
Xuong, Ng. D. See Buu-Hoï, Ng. Ph., **1358**
Zealley, J. See Duncanson, L. A., **1331**.

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271. *Supposed Rotational Isomerism in the Succinic Acid Series.*

By G. D. Buckley.

The existence (Duncanson, *J.*, 1952, 1753) of two solid forms of (±)-methylsuccinic acid has been confirmed and a third form has been discovered. The three are readily interconvertible and the differences between them disappear on dissolution or fusion. It is therefore concluded that these three forms are polymorphic modifications and not rotational isomers as claimed by Duncanson.

Duncanson (*J.*, 1952, 1753) reported that certain monosubstituted succinic acids exist in two forms, of which he obtained one by crystallisation and the other by sublimation. The two forms have different infra-red absorption spectra in the solid state and he considers that they are rotational isomers.

The discovery of a new form of isomerism is an event of some importance requiring support by irrefutable evidence. Very many carboxylic acids exist in two or more polymorphic modifications, but it has not so far been suggested that these are rotational isomers. Indeed acetic acid which is dimorphic, and malonic and anthranilic acids which are trimorphic, offer no possibility of isomerism, rotational or otherwise. Furthermore, according to Kendall (Amer. Chem. Soc. Meeting, Boston, Mass., April, 1951) the polymorphic modifications of a compound commonly have different infra-red absorption spectra, and Ebert and Gottlieb (*J. Amer. Chem. Soc.*, 1952, **74**, 2806) have shown that the differences in the spectra of the three forms of anthranilic acid are very marked. It therefore seems reasonable to suppose that the two forms of (±)-methylsuccinic and (±)-chlorosuccinic acid are also polymorphic modifications unless evidence to the contrary can be adduced.

Most of Duncanson's evidence relates to (±)-methylsuccinic acid. He states that the " crystallised acid " (modification A) is the normal form, which is recovered unchanged on crystallisation from water or from a mixture of chloroform and light petroleum, but is converted into the " sublimed acid " (modification B) by sublimation *in vacuo*. He found that B was recovered unchanged on crystallisation from benzene, but was reconverted into A when dissolved in water and boiled for several hours. He states, however, that he recovered B unchanged after 30 minutes' refluxing of its aqueous solution and evaporation at room temperature.

These observations, although suggestive of isomerism, do not rule out polymorphism. The essential distinction between these two is that the differences between polymorphic forms are confined to the solid state and disappear when the substances are melted or dissolved, whereas the differences between isomeric forms are also manifest, at least temporarily, in the liquid state. In order to prove that A and B are isomers it must therefore be demonstrated that both can exist in solution or in the liquid state, and this Duncanson purports to have done by showing that A and B have different dipole moments in benzene solution.

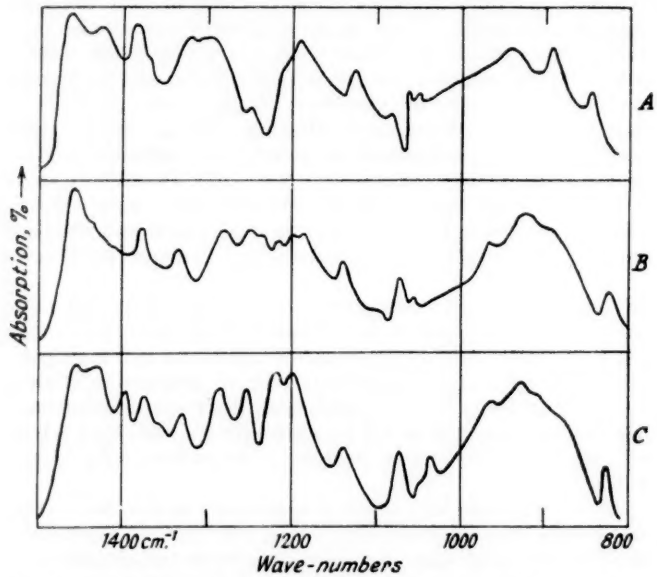
Modification A.						*Modification B.*					
10^2c.	ε_s	P_M	P_R	P_O	μ (D)	10^2c.	ε_s	P_M	P_R	P_O	μ (D)
6·092	2·2735	26·3	28·35	0	0	6·212	2·2742	45·1	28·35	16·75	0·90
6·169	2·2738	34·0	28·35	5·65	0·52	6·289	2·2745	52·5	28·35	24·15	1·08

However, his experimental results, which are reproduced above, will not stand up to critical examination. The determinations were carried out at such low concentrations that a slight error in the measurement of the dielectric constant would result in a large error in the dipole moment. That such errors must have occurred is evident from the large discrepancy between the two results for modification A and from the fact that this discrepancy is larger than the difference between the second value of the dipole moment for A and the first value for B. Furthermore the figure of 0 given for the dipole moment of A in the first determination is spurious: the true figure for P_0 is $-2{\cdot}05$, and a dipole moment cannot be calculated from it. A further defect of these results is that the dipole

moments were calculated from a single dielectric-constant measurement in each case, whereas it is well known that the total polarisation and therefore the apparent dipole moment frequently varies with concentration; results should be obtained at several concentrations and extrapolated to infinite dilution. Bearing all these considerations in mind it must be concluded that the dipole-moment results are of little value and certainly cannot be adduced as evidence that A and B give different solutions.

Duncanson's theory cannot however be dismissed merely on the grounds that he has failed to provide evidence which supports it, and the different forms of (±)-methylsuccinic acid have therefore been prepared and studied. Modifications A and B were prepared according to Duncanson, and his observation that they had different infra-red absorption spectra in the solid state was confirmed (see Figure). They also had very different *X*-ray powder patterns. Form A was stable at room temperature, but B, after 2 months at room

Infra-red absorption spectra of three modifications of (±)-methylsuccinic acid, measured as a 20% suspension in Nujol. Cell thickness 0·025 mm.



temperature, had changed to a third modification (C) which had an infra-red absorption spectrum (see Figure) and an *X*-ray pattern which differed from those of both A and B. Form C was itself stable at room temperature.

All three forms when melted and cooled reverted to A, the highest-melting modification. It may therefore be assumed that the differences between them disappear on melting. All three invariably gave B when crystallised from benzene or ether and, except in one case, A when crystallised from water. In a single experiment, B was dissolved in a little hot water and seeded with B; the crystals obtained from the solution were pure C. When form A or B was dissolved in the minimum of cold water and evaporated *in vacuo* over phosphoric oxide at 20°, the product was pure A in both cases; Duncanson's statement that long boiling was necessary to effect the change from B to A could not be confirmed. In no case was B isolated from an aqueous solution. Crystallisation of any form from chloroform gave sometimes B and sometimes C, but C could always be obtained from solutions in chloroform by seeding with C.

These results show the characteristic behaviour of a trimorphic compound, but they do not rule out the possibility of labile isomerism. In order to eliminate this possibility it is necessary to prove that the three forms give identical solutions, and evidence bearing on this point was therefore sought.

Some difficulty was encountered in finding a suitable solvent for infra-red absorption measurements. The acid is very soluble in oxygen-containing solvents but these all absorb strongly in the infra-red in the same region as the acid itself, whereas the solubility in hydrocarbons and chlorinated hydrocarbons, which would otherwise be very suitable, is much too low. However, acetonitrile, in which methylsuccinic acid is very soluble, was fairly satisfactory since its absorption spectrum shows no bands in the region 1350—1090 cm.$^{-1}$ where the acid absorbs strongly and where the main differences between the three solid forms appear. 10% Solutions of the three modifications in this solvent had identical absorption spectra.

According to Sidgwick (*J.*, 1915, **107**, 672), when a substance is added to a saturated solution of another substance of the same molecular formula at constant temperature, then if they are isomers, the solid will dissolve, whereas if they are polymorphs the solid will not dissolve and the concentration of the solution will remain the same or decrease. Since Sidgwick demonstrated that this method distinguishes polymorphism from structural, geometrical, and optical isomerism it should be effective in detecting rotational isomerism. All three forms of (±)-methylsuccinic acid are readily soluble in ether and the concentration may be determined by titration with alkali. In this way it was shown that the addition of B or C to a saturated solution of A in ether produced no increase in the amount of acid in solution.

It is therefore proved beyond reasonable doubt that only one modification of (±)-methylsuccinic acid exists in solution or in the liquid state and that the three solid forms are polymorphic modifications and not rotational isomers.

Experimental

Microanalyses are by Dr. A. F. Colson. M. p.s are corrected.

Preparation of Polymorphic Modifications of (±)-Methylsuccinic Acid.—Modification A. (±)-Methylsuccinic acid, prepared according to *Org. Synth.*, 1946, **26**, 54 and crystallised from water, had m. p. 113—114°, and appeared to be identical with the " crystallised acid " described by Duncanson (*loc. cit.*) (Found: C, 45·5; H, 6·1. Calc. for $C_5H_8O_4$: C, 45·4; H, 6·1%).

Modification B. A specimen of A was sublimed at 95°/2 × 10^{-3} mm. The sublimate, m. p. 108—110°, was apparently identical with Duncanson's " sublimed acid " (Found: C, 45·3; H, 6·0%).

Modification C. This modification was first obtained fortuitously, but was later prepared by dissolving A in boiling chloroform, seeding the solution with a crystal of C, allowing it to cool, and collecting the crystals, m. p. 111—112° (Found: C, 45·4; H, 6·0%).

Infra-red Spectrography.—The infra-red absorption spectra were measured by Mr. L. H. Cross, using a Grubb-Parsons model S3 spectrometer, equipped with a rock-salt prism, thermal detector, A.C. amplifier, and pen recorder.

The spectra of the three forms in the solid state were measured on 20% suspensions in Nujol at a cell thickness of 0·025 mm. The spectra of A and B (see Figure) were similar in general form to those of Duncanson's " crystallised " and " sublimed " acids respectively, but differences in detail were noticeable.

X-Ray Examination.—The three modifications were examined by Mr. R. Brooks and Mr. T. C. Alcock by normal powder methods, using a 9-cm. Bradley–Jay type camera and nickel-filtered Cu-$K\alpha$ radiation. The photographs indicated different crystal structures. A showed two characteristic reflections of equal strength at 4·34 and 4·11 Å; B showed a strong reflection at 4·81 Å, and C a strong reflection at 4·51 Å.

Interconversion of the Three Forms.—After various treatments, the products were characterised by infra-red spectrography. Some results are recorded on p. 1326. When kept for 2 months at 15—25°, A and C were unchanged, but B had been transformed into C; each form was unchanged after 6 hours at 60°. Form B was obtained when a solution of A or B in ether was evaporated at 20°.

One part of a solution of B in water was cooled, seeded with a crystal of A, and kept at 0—5° until crystallisation was complete; the crystals were pure A. The second part of the solution was similarly seeded with B; it gave pure C. In an attempt to repeat this result, both solutions gave pure A. Solutions of A in benzene, similarly seeded with A or B, gave only B. A solution of A in chloroform, when seeded with B, deposited B, but when seeded with A deposited C. When this experiment was repeated both solutions deposited only C.

Additive Solubilities in Ether.—Finely-powdered A (14 g.) was stirred in pure dry ether (80 c.c.) at 23° (thermostat). After 1 hour the undissolved solid was allowed to settle. 5 Ml. of the solution were withdrawn, run into distilled water, and titrated with 0·5N-sodium hydroxide (phenolphthalein). The stirrer was restarted and further 5-ml. portions were withdrawn at half-hourly intervals until no increase in titre occurred. Final titres: 20·55, 20·45 ml.; *i.e.*, 135·3 g. of acid per l. Finely-divided B (2 g.) was then added, stirring was continued for 30 minutes, and a 5-ml. portion was withdrawn. Titration required 20·55 ml. Finely-divided C (2 g.) was then added and the procedure repeated. Titration required 20·5 ml.

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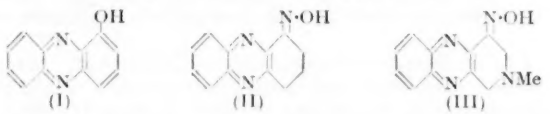
272. 1-*Acetamidophenazine*, 5 : 8 : 13 : 14-*Tetra-azapentaphene*, *and* 5 : 6 : 8 : 13 : 14-*Penta-azapentaphene*.

By GERALD H. COOKSON.

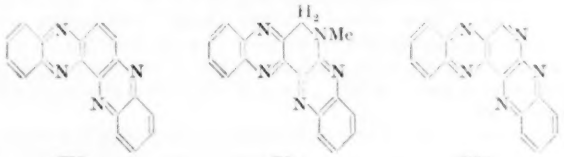
Wolff aromatization of 1 : 2 : 3 : 4-tetrahydro-1-hydroxyiminophenazine (II) gives 1-acetamidophenazine, but a similar dehydration of the more nitrogenous analogue (III) was not realized; (II) and (III) react with *o*-phenylenediamine giving products from which the two aza-hydrocarbons (IV) and (VI) mentioned in the title are obtained.

THE recent synthesis of the powerful fungicide hemipyocyanine (1-hydroxyphenazine) (I) by Hegedüs (*Helv. Chim. Acta*, 1950, **33**, 766) involved 1-aminophenazine in the penultimate stage and avoided the difficulties of the original method (cf. Surrey, *Org. Synth.*, 1946, **26**, 86). However, although fairly good yields of 1-aminophenazine can be obtained by cyclization of appropriate aminodiphenylamines (Albert and Duewell, *J. Soc. Chem. Ind.*, 1947, **66**, 11; Hegedüs, *loc. cit.*), several steps are required to obtain the starting materials, a disadvantage which does not apply to the method to be described.



(I) (II) (III)

o-Phenylenediamine condenses rapidly with one molecule of bishydroxyiminocyclohexanone to form 1 : 2 : 3 : 4-tetrahydro-1-hydroxyiminophenazine (II) (Borsche, *Zentr.*, 1909, II, 1549). This is dehydrated and acetylated by boiling acetic anhydride, giving 1-acetamidophenazine in an overall yield of about 30% based on the diamine (for a review of this type of reaction see Horning, *Chem. Reviews*, 1943, **33**, 89). A Beckmann rearrangement, which may take place instead of aromatization (Schroeter, *Ber.*, 1930, **63**, 1308; Horning, Stromberg, and Lloyd, *J. Amer. Chem. Soc.*, 1952, **74**, 5153), was not observed in this case though it may have been responsible for the variable yields. 1-Acetamidophenazine has previously been prepared by removal of the amino-group from 1-acetamido-3-aminophenazine (Kehrmann and Prunier, *Helv. Chim. Acta*, 1924, **7**, 984). It was



(IV) (V) (VI)

identified by hydrolysis and comparison with an authentic specimen of the 1-amino-compound. The hydrochloride of (III) was prepared from 3 : 5-bishydroxyimino-1-methylpiperid-4-one hydrochloride in an analogous way to (II) but preliminary experi-

ments with acetic anhydride were not promising. It had been hoped that a quaternary salt of the azaphenazine might have been formed.

When bishydroxyimino*cyclo*hexanone was boiled with two equivalents of *o*-phenylenediamine in acetic acid, the intermediate (II) reacted further to give a pentacyclic compound in high yield. The deeply coloured primary product, which may have been a " phenazhydrin " or a quinonoid dihydro-compound, soon suffered atmospheric oxidation to the pale yellow 5 : 8 : 13 : 14-tetra-azapentaphene (IV). Its absorption spectrum (Fig. 1)

FIG. 1. FIG. 2.

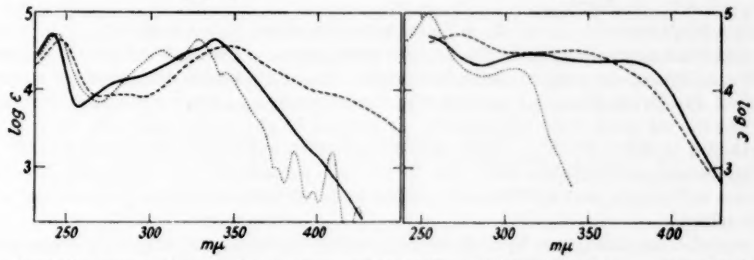


FIG. 1. *Absorption curves of* 5 : 8 : 13 : 14-*tetra-azapentaphene* (IV) *in ethanol* (———) *and in* 3·2N-HCl–EtOH (– – –), *and of* 5 : 8-*diazapentaphene* (. . . .) (*Badger and Pettit,* J., 1952, 1874).

FIG. 2. *Absorption curves of* 6 : 7-*dihydro*-6-*methyl*-5 : 6 : 8 : 13 : 14-*penta-azapentaphene* (V) *in chloroform* (———) *and in* 0·17N-HCl–$CHCl_3$ (– – –), *and of* 2 : 2′-*dinaphthyl in ethanol* (. . . .) (*Friedel and Orchin, " U.V. Spectra of Aromatic Compounds," Wiley,* 1951, 309).

closely resembles that of 5 : 8-diazapentaphene although the fine structure has been lost (cf. Badger, Pearce, and Pettit, *J.*, 1951, 3199).

A similar condensation between two molecules of the diamine and one of 3 : 5-bishydroxyimino-1-methylpiperid-4-one hydrochloride took place less readily and gave a very weak base assumed to be 6 : 7-dihydro-6-methyl-5 : 6 : 8 : 13 : 14-penta-azapentaphene (V) but not fully investigated. Elementary analysis gave inconsistent results. The absorption spectrum in neutral and acid chloroform is shown in Fig. 2 together with that

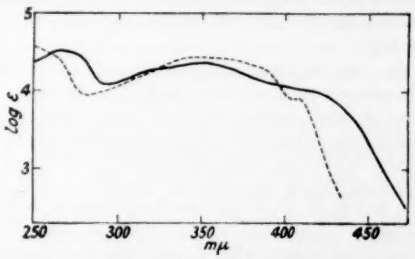


FIG. 3. *Absorption curves of* 5 : 6 : 8 : 13 : 14-*penta-azapentaphene* (VI) *in chloroform* (———) *and in* 0·17N-HCl–$CHCl_3$ (– – –).

of 2 : 2′-dinaphthyl. The cation of (V) compared with the latter has maxima shifted by 18 mμ and 34 mμ towards longer wave-lengths, a bathochromic effect expected from the addition of the alicyclic bridge (Jones, *J. Amer. Chem. Soc.*, 1941, **63**, 1658) provided $N_{(6)}$ has accepted a proton. Absorption would also be expected to begin at longer wave-lengths owing to the four nitrogen atoms in the quinoxaline rings. The formation of (V) from the starting material involves the loss of water, two molecules of hydroxylamine, and four hydrogen atoms. Ammonium chloride was identified in the reaction mixture, although it is not clear whether this arose from the reduction of hydroxylamine or in some other way.

Vacuum-sublimation of (V) from palladium–charcoal gave a dark green product which was oxidized with hot nitrobenzene to 5 : 6 : 8 : 13 : 14-penta-azapentaphene (VI). This formed bright yellow crystals which appeared unchanged even when heated to 365° in an open capillary. The brilliant turquoise fluorescence shown by neutral but not acid solutions of (VI) may have somewhat flattened the absorption maximum at 348 mμ which was measured without special precautions (Fig. 3).

Experimental

1 : 2 : 3 : 4-Tetrahydro-1-hydroxyiminophenazine (II) separated in 65% yield after equimolecular quantities of *o*-phenylenediamine and bishydroxyimino*cyclo*hexanone had been boiled in water or acetic acid for 15 minutes; it formed platelets (from pyridine), m. p. 213° (efferv.; m. p. higher with quick heating) (Found: C, 67·6; H, 5·2; N, 19·8. Calc. for $C_{12}H_{11}ON_3$: C, 67·6; H, 5·2; N, 19·7%). The 2 : 4-*dinitrophenylhydrazone* crystallized from pyridine in light brown needles which lost solvent of crystallization at 80°/0·2 mm. (20 hours), and had m. p. 249—251° (efferv.) (Found: C, 56·75; H, 4·1; N, 21·9. $C_{18}H_{14}O_4N_6$ requires C, 57·15; H, 3·7; N, 22·2%).

1-*Acetamidophenazine*.—1 : 2 : 3 : 4-Tetrahydro-1-hydroxyiminophenazine (1 g.) was boiled under reflux with acetic anhydride (10 c.c.) for 30 minutes. The dark solution was poured into water (30 c.c.), excess of sodium carbonate added, and the mixture extracted with chloroform. The washed and dried (Na_2SO_4) extract was run through an alumina column from which the product was eluted with dried chloroform; it formed bright yellow crystals, m. p. 170—172°, from methanol or ethyl acetate. The yield in a typical experiment was 0·45 g. (40%), but it varied in different runs between 25% and 75%. The presence of dry hydrogen chloride during the reaction led to tars, and addition of pyridine or fused sodium acetate to the acetic anhydride had little effect.

The acetyl compound was hydrolysed by boiling hydrochloric acid to 1-aminophenazine, deep red prisms (from methanol), m. p. 179—181° undepressed by admixture with an authentic sample kindly supplied by Professor Albert.

3 : 5-*Bishydroxyimino*-1-*methylpiperid*-4-*one hydrochloride* crystallized when excess of ethyl nitrite was passed into a solution of the piperidone (2 g.) in acetic acid (5 c.c.) containing concentrated hydrochloric acid (2·5 c.c.). The product (2·28 g., 75%) was recrystallized from water and dried (P_2O_5) at 20°/0·2 mm. for 24 hours before analysis, but it gave unsatisfactory results. It darkened at 180° and carbonized with gas evolution at *ca.* 195° without melting (Found: C, 32·25; H, 5·2; N, 19·6. $C_6H_{10}O_3N_3Cl,\frac{1}{2}H_2O$ requires C, 33·25; H, 5·1; N, 19·4%).

1 : 2 : 3 : 4-*Tetrahydro*-4-*hydroxyimino*-2-*methyl*-2 : 9 : 10-*triaza*-*anthracene Hydrochloride* (III).—The foregoing hydrochloride (0·8 g.) and *o*-phenylenediamine (1·0 g.) were boiled in ethanol (5 c.c.) for 10 minutes by which time the *product* (0·35 g.) had crystallized in pale brown blades. These, being very soluble in water but almost insoluble in organic solvents, were merely washed with hot alcohol and dried before analysis. They darkened at *ca.* 190° but did not melt (Found: C, 54·45; H, 5·1; N, 20·5. $C_{12}H_{13}ON_4Cl$ requires C, 54·4; H, 4·9; N, 21·2%).

5 : 8 : 13 : 14-*Tetra-azapentaphene* (IV).—*o*-Phenylenediamine (1·0 g.) and bishydroxyimino*cyclo*hexanone (0·55 g.) were boiled with acetic acid (5 c.c.) until the brown solution suddenly became deeply coloured (5—10 min.) and brown needles (0·95 g.) separated. The heat of crystallization made the mixture boil violently. The brown product gave dark blue or green solutions in organic solvents which slowly changed to yellow on atmospheric oxidation. This was accomplished rapidly by chemical means such as recrystallization from nitrobenzene. After a few days in air the brown crystals had become yellow; they had m. p. 300—303°. Traces of impurity were removed by chromatography on alumina in chloroform. The same product was obtained when the tetrahydrohydroxyiminophenazine was boiled in acetic acid with *o*-phenylenediamine. 5 : 8 : 13 : 14-*Tetra-azapentaphene* formed pale yellow needles containing one mol. of chloroform of crystallization, which was rapidly lost under reduced pressure. A solvent-free sample, obtained by sublimation at 270°/0·2 mm., had m. p. 304° [Found: C, 76·4; H, 3·5; N, 19·9%; *M* (Rast), 274 ± 14. $C_{18}H_{10}N_4$ requires C, 76·6; H, 3·55; N, 19·9%; *M*, 282. Loss of $CHCl_3$ on warming at 0·1 mm.: 0·97, 1·0 mol.]. The ultra-violet absorption spectrum in ethanol showed maxima at 242 mμ (log ε 4·71) and 339 mμ (log ε 4·64), which moved to 246 mμ (log ε 4·64) and 348 mμ (log ε 4·56) in 3·2N-ethanolic hydrogen chloride. Diffuse absorption in the blue region gave the acid solution a yellow colour.

The *picrate* crystallized in brown rods from ethylene dibromide. It was easily decomposed by water and melted indistinctly at *ca.* 240—265° (Found: C, 56·0; H, 2·9; N, 18·8. $C_{18}H_{10}N_4,C_6H_3O_7N_3$ requires C, 56·4; H, 2·5; N, 19·2%).

5 : 6 : 8 : 13 : 14-*Penta-azapentaphene* (VI).—A solution of 3 : 5-bishydroxyimino-1-methylpiperid-4-one hydrochloride (0·9 g.) and *o*-phenylenediamine (1·0 g.) in acetic acid (5 c.c.) was boiled for 30 min., and most of the solvent was then removed under reduced pressure and replaced by ethanol. The brown precipitate (0·25 g.) which separated overnight was washed free from ammonium chloride with water. Repeated recrystallization from nitrobenzene

provided pale buff prisms believed to be 6 : 7-*dihydro*-6-*methyl*-5 : 6 : 8 : 13 : 14-*penta-aza-pentaphene* (V) although after washing with alcohol and 24 hours' drying at 100°/0·3 mm. inconsistent analyses were obtained from the same sample (Found : C, 73·2, 72·6; H, 3·6, 3·7; N, 21·8, 22·6. $C_{18}H_{13}N_5$ requires C, 72·3; H, 4·4; N, 23·4%). Sublimation of the pure compound or the crude product at 330°/0·2 mm., best after admixture with acid 10% palladium-charcoal, gave a green product which was oxidized by recrystallization from nitrobenzene to 5 : 6 : 8 : 13 : 14-*penta-azapentaphene*, yellow crystals which did not melt or discolour at 365° (Found : C, 72·1; H, 3·2; N, 24·2. $C_{17}H_9N_5$ requires C, 72·1; H, 3·2; N, 24·7%). A solution in chloroform showed absorption maxima at 265 and 348 mμ (log ε 4·52 and 4·36) and in chloroform containing hydrogen chloride at 351 and 407 mμ (log ε 4·44 and 3·91). The maxima for (V) were at 317 and 368 mμ (log ε 4·48 and 4·39), and in acid chloroform at 272 and 340 mμ (log ε 4·72 and 4·51). The intense turquoise fluorescence of (VI) in neutral solution was quenched by acid; the dihydromethyl compound (V) did not fluoresce. In some experiments (V) was partly converted into (VI) without sublimation and could not be obtained pure.

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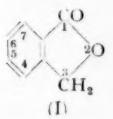
273. *Infra-red Spectroscopy and Structural Chemistry. Part V. Hydroxyphthalides.*

By L. A. DUNCANSON, JOHN FREDERICK GROVE, and (MRS.) J. ZEALLEY.

4- and 7-Hydroxyphthalides may be distinguished by their infra-red spectra in dilute solution, wherein intramolecular hydrogen bonding in 7-hydroxyphthalides causes a characteristic lowering of the C=O stretching frequencies.

IT is well established that αβ-unsaturated γ-lactones, as in phthalide (I), have C=O stretching frequencies near 1750 cm.$^{-1}$ in the solid state (Grove and Willis, *J.*, 1951, 877). In addition, many examples are known of the behaviour of pure substances containing the *o*-hydroxyaroyl structure wherein strong intramolecular hydrogen bond formation causes both the hydroxyl and the carbonyl stretching frequencies to be markedly lower than those of the corresponding methyl ethers or non-hydroxylated compounds (Flett, *J.*, 1948, 1441; Hunsberger, *J. Amer. Chem. Soc.*, 1950, **72**, 5626). These decreases persist in dilute solution in a non-polar solvent, and, since similar effects are not observed in the corresponding *m*- and *p*-hydroxy-compounds (Martin, *Nature*, 1950, **166**, 474), have been used to detect chelation. However, Grove (*Biochem. J.*, 1952, **50**, 648), in attempting to apply this to the orientation of hydroxyphthalides of unknown constitution, found little difference between the C=O frequencies of 7-methoxy- and 7-hydroxy-4 : 6-dimethylphthalide in the solid state, and Hochstein and Pasternack (*J. Amer. Chem. Soc.*, 1952, **74**, 3905) commented on the similarity of the spectra of 7- and 4-hydroxy-3-methylphthalide although they report significant differences between the C=O frequencies of 7-methoxy- and 7-hydroxy-3-methylphthalide in chloroform solution. The present paper reports a systematic examination of the infra-red spectra of 7- and 4-hydroxyphthalides in the solid state and in solution, and shows how these compounds may be distinguished.



(I)

EXPERIMENTAL

Materials.—4-Hydroxyphthalide, m. p. 254—260° (decomp.), and 4-methoxyphthalide, m. p. 127°, were prepared by the method of Buehler, Powers, and Michels (*J. Amer. Chem. Soc.*, 1944, **66**, 417) who established their structures by unambiguous syntheses.

7-*Methoxyphthalide* was prepared by reduction of 3-methoxyphthalic anhydride with zinc and acetic acid in concentrated hydrochloric acid. It was separated from the 4-methoxyphthalide, which is formed simultaneously, by recrystallisation from methanol and then from benzene–

* Part IV, *J.*, 1953, 1207.

light petroleum, to give colourless prisms, m. p. 96° (Found: C, 65·85; H, 5·1; OMe, 18·9. $C_9H_8O_3$ requires C, 65·85; H, 4·9; OMe, 19·0%).

Demethylation with hydrobromic acid and crystallisation of the product from water gave 7-hydroxyphthalide, m. p. 132° (Found: C, 63·75; H, 4·0. Calc. for $C_8H_6O_3$: C, 64·0; H, 4·0%), which gave an intense blue colour with ferric chloride in aqueous or ethanolic solution. Vêne and Tirouflet (*Compt. rend.*, 1951, **232**, 2329) give m. p. 128—129°.

7-Hydroxy-, m. p. 158°, and 7-methoxy-4 : 6-dimethylphthalide, m. p. 113° (Raistrick and Ross, *Biochem. J.*, 1952, **50**, 635), were obtained by degradation of gladiolic acid (Grove, *loc. cit.*). Purified phthalide, m. p. 73°, methyl *m*-hydroxybenzoate, m. p. 70°, and methyl salicylate, n_D^{20} 1·537, were used.

Infra-red Spectra.—The spectra were measured with a Grubb Parsons S 3A spectrometer. The case of the instrument was sealed and dry air circulated through it. Solids were examined as "Nujol" mulls, and the solutions were all approx. 0·02M, except for 7-hydroxyphthalide which was 0·005M in carbon tetrachloride. Carbonyl frequencies in solution were measured with a rock-salt prism and path lengths of 0·25 mm.; a lithium fluoride prism and path lengths varying between 0·25 and 5 mm. were used for the measurement of -OH stretching frequencies. Accuracy: ±3 cm.$^{-1}$.

Solvents.—"AnalaR" carbon tetrachloride was distilled over phosphoric oxide before use. Chloroform containing about 1% of ethanol as a stabiliser was dried and distilled before use, but the ethanol was not removed. Dioxan was purified according to Hess and Frahm's method (*Ber.*, 1938, **71**, 2627).

Results and Discussion

The annexed Table lists the carbonyl stretching frequencies of some hydroxyphthalides, as solids and in dilute solution in carbon tetrachloride, dioxan, and chloroform. The corresponding figures for phthalide itself are included.

Carbonyl stretching frequencies of some phthalides as solids and in solution.

Phthalide	Solid	Solution in CCl_4	Solution in dioxan	Solution in $CHCl_3$
7-Hydroxy-4 : 6-dimethyl-	1737	1747	1750	1734
7-Hydroxy-	1726	1749	1754	1738
4-Hydroxy-	1723	Insol.	1772	1760
7-Methoxy-4 : 6-dimethyl-	1749	1771	1768	1756
7-Methoxy-	1748	1782	1772	1754
4-Methoxy-	1765	1783	1774	1764
Phthalide	1752	1778	1770	1761

In the solid state 4- and 7-hydroxyphthalide absorb at lower frequencies than do the corresponding methyl ethers, and the lactone C=O frequency cannot be correlated with the proximity of the hydroxyl and carbonyl groups in the molecule. However, the frequencies found for the dioxan solutions fall into two groups, namely, those near 1750 cm.$^{-1}$, characteristic of 7-hydroxyphthalides, and those near 1770 cm.$^{-1}$, given by the remainder.

These results are closely paralleled by those obtained from solutions in carbon tetrachloride and in chloroform. In carbon tetrachloride the 7-hydroxyphthalides again absorb near 1750 cm.$^{-1}$ while the remainder absorb at higher frequencies, in this case near 1780 cm.$^{-1}$. 4-Hydroxyphthalide is too insoluble for measurement even when using a 1 cm. thickness of a saturated solution, but from its carbonyl frequency in dioxan solution it is reasonable to predict that a dilute solution in carbon tetrachloride of a 4-hydroxyphthalide should show carbonyl absorption near 1780 cm.$^{-1}$. In chloroform the carbonyl frequencies are all lower than in the other two solvents, the 7-hydroxy-compounds absorbing near 1735 cm.$^{-1}$ and the others between 1755 and 1765 cm.$^{-1}$.

A further distinction can be found between 7-hydroxyphthalides and the remainder by comparing their respective carbonyl frequencies in two of the solvents used; the 7-hydroxy-compounds have a slightly lower frequency in carbon tetrachloride than in dioxan, while the remainder show a difference of 5—10 cm.$^{-1}$ in the opposite direction.

The hydroxyl stretching frequencies of three hydroxyphthalides are as follows:

7-Hydroxy-4 : 6-dimethyl-		*7-Hydroxy-*		*4-Hydroxy-*	
Solid	In CCl_4	Solid	In CCl_4	Solid	In CCl_4
3405	3420	3490	3420	3190 broad	Insol.
3340 weak	—	3402	—	—	—

There are insufficient data to enable structural correlations to be made. It can be seen, however, that 4-hydroxyphthalide is strongly bonded in the solid state, the band with a peak at 3190 cm.$^{-1}$ being very broad and extending from 3100 to 3300 cm.$^{-1}$ approximately. It is probable that a dilute solution of a soluble 4-hydroxyphthalide in carbon tetrachloride would absorb near 3600 cm.$^{-1}$, as does methyl *m*-hydroxybenzoate. The 7-hydroxyphthalides absorb at much lower frequencies than this.

The interpretation of the above results is straightforward. In the solid state both types of hydroxyphthalide studied form hydrogen bonds between their hydroxyl and carbonyl groups. In dilute solutions the intermolecular bonds dissociate and the 7-hydroxyphthalides contain weak intramolecular bonds. This behaviour is somewhat different from that observed with hydroxybenzoic esters wherein intramolecular hydrogen bonds are much stronger. The carbonyl and hydroxyl stretching frequencies of methyl salicylate and methyl *m*-hydroxybenzoate as pure substances and as 0·02M-solutions are as follows :

	Methyl m-*hydroxybenzoate*				*Methyl salicylate*		
	Pure substance	In CCl_4	In dioxan		Pure substance	In CCl_4	In dioxan
OH ...	3340	3580	—	OH...	3184 (broad)	3198 (broad)	—
	3361 (shoulder)	3437 (broad)	—	CO ...	1678	1681	1683
CO ...	1695	1728	~1722				
	—	1702	—				

When the hydroxy-group is *ortho* to the carbomethoxy-group, a strong intramolecular hydrogen bond is formed between them, both in the pure state and in solution.

The spectrum of *m*-hydroxybenzoic ester in solution has two carbonyl and two hydroxyl bands due to the presence of an equilibrium between non-bonded molecules and intermolecularly bonded ones. It is interesting that, like the hydroxyphthalides, the intramolecularly bonded *o*-hydroxybenzoate shows a slight increase and the non-associated *m*-hydroxybenzoate a decrease in carbonyl frequency on changing from carbon tetrachloride to dioxan as solvent.

The difference in behaviour of the *o*-hydroxyphthalides and benzoates must be connected with the strained 5-membered ring present in the former. Molecular models show that in 7-hydroxyphthalide, strain in the lactone ring bends the carbonyl group away from the hydroxyl group to an extent requiring a C–H–O distance approaching 3 Å. This is near the limit for hydrogen-bond formation (Pauling, " Nature of the Chemical Bond," Oxford Univ. Press, London, 2nd Edn., p. 289) and a bond of this length would be expected to be weak. It is apparent that intermolecular hydrogen bonding in solid 4-hydroxyphthalide is as strong as bonding in solid 7-hydroxyphthalide and therefore spectra of Nujol " mulls " should not be used for detecting chelation in hydroxyaroyl compounds of unknown orientation. The necessary information can, however, be obtained from the spectra of dilute solutions.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, BUTTERWICK RESEARCH LABORATORIES,
THE FRYTHE, WELWYN, HERTS. [*Received, January* 14*th*, 1953.]

274. *Substituted Benzidines and Related Compounds as Reagents in Analytical Chemistry. Part XII.* Reagents for the Precipitation of Sulphate.*

By R. Belcher, A. J. Nutten, and W. I. Stephen.

The sulphates of the 4-amino-4′-halogenodiphenyls have been prepared, and their solubilities in water determined. The values obtained are considerably less than those for 4-amino- and 4 : 4′-diamino-diphenyl. One compound, 4-amino-4′-chlorodiphenyl, has the least soluble sulphate and has been developed as a new reagent for the rapid and accurate alkalimetric determination of the sulphate ion. Interferences are few; in particular, the nitrate ion has no effect. The reagent is simply prepared and is readily and completely recovered after use.

The solubility of benzidine sulphate has been determined by several workers. Recently, Belcher and Nutten (*J.*, 1951, 544) showed that none of the sulphates of several nuclear-substituted 4 : 4′-diaminodiphenyls is less soluble than benzidine sulphate. The solubility of 4-aminodiphenyl sulphate is comparable with that of benzidine sulphate (*loc. cit.*), and it is evident that the diamino-structure of benzidine is not an essential cause of insolubility of sulphates. The presence of one amino-group is sufficient provided it occupies one of the available *para*-positions in the diphenyl nucleus: the sulphates of both 2 : 4′-diaminodiphenyl (diphenyline) and 2-aminodiphenyl are more soluble than those of the corresponding *para*-substituted bases.

Belcher and Nutten had shown (*loc. cit.*) that no simple weighting effect was apparent from their examination of alkylbenzidines. The properties of 4-aminodiphenyl are similar in precipitation reactions to those of 4 : 4′-diaminodiphenyl (benzidine). The former has the 4′-position available for substitution, and it was decided to examine the effect of halogen in this position because its introduction would appreciably increase the molecular weight. It was thought that sulphates less soluble than that of 4-aminodiphenyl would be obtained, the solubility decreasing with increase in molecular weight. Accordingly, 4-amino-4′-chloro- and -4′-bromo-diphenyl were prepared, and the solubilities of their sulphates, determined by Belcher and Nutten's method (*loc. cit.*), were much less than those of benzidine or 4-aminodiphenyl and were, moreover, in the reverse of the order, Br < Cl, to be expected from a weighting effect.

This reversal appeared to indicate that an electronic effect was exerting an influence on the lattice energy of the sulphate crystal which, in turn, influenced its solubility. The crystals of the 4-aminodiphenyl sulphates under investigation may be considered to be built of units of $X{\cdot}C_6H_4{\cdot}C_6H_4{\cdot}\overset{+}{N}H_3{\cdot}\overset{--}{SO_4}{\cdot}\overset{+}{N}H_3{\cdot}C_6H_4{\cdot}C_6H_4X$, where X = hydrogen or halogen. The lattice energy of such a crystal will be affected by any alteration of the electrostatic forces binding the sulphate ion, and the van der Waals forces binding adjacent units. The inductive and mesomeric effects which arise when halogen is introduced into the molecule must affect these forces in the crystal structure and may result in a considerable alteration of the lattice energy for the different substituents. Thus, the inductive effect should result in an increase in lattice energy by increasing the electrostatic forces binding the sulphate ion and so should decrease the solubility, whilst the mesomeric effect, acting in opposition, should cause an increase in solubility. The van der Waals forces are much weaker than the electrostatic forces and may be ignored, as it is evident that the inductive and mesomeric effects also contribute greatly to the binding of adjacent units.

The solubilities of the sulphates of 4-aminodiphenyl and its four 4′-halogeno-derivatives appear to depend on the relative values of the inductive and mesomeric effects, and an examination of these values for hydrogen and the halogens should indicate the order of these solubilities. However, no values which would allow the comparison of their magnitudes have been recorded, although various expressions have been proposed for each effect, separately.

* Part XI, *J.*, 1952, 2438.

The solubilities found for all four halogeno-base sulphates were less than that of the 4-amino-sulphate, the salt of 4-amino-4′-chlorodiphenyl being the least soluble; the order was: Cl<Br<F<I<H. However, van Hove (*Bull. Sci. Acad. roy. Belg.*, **1922**, **2**, 524) has reported the solubility of 4-amino-4′-fluorodiphenyl sulphate to be 200 mg./l., *i.e.*, much greater than that of 4-aminodiphenyl; in the absence of details of van Hove's work, this discrepancy cannot be explained. The following Table lists the solubilities (*S*, in mg./l. at 25°) of the various sulphates. The analytical data show that only the normal sulphates were examined; van Hove may have obtained an acid sulphate of higher solubility. The amounts of sulphate left in solution are included for comparison.

Analyses and solubilities of sulphates.

4-Aminodiphenyl	Found, %				Calc., %				*S*	SO_4^{2-} left in soln., mg./l.
	C	H	N	S	C	H	N	S		
(Unsubstituted) ..... 4′-Amino-	(See Belcher and Nutten, *loc. cit.*)								130 98	28·6 33·4
4′-Iodo-	42·1	3·1	4·1	4·6	42·0	3·2	4·1	4·7	110	15·3
4′-Fluoro-	61·1	4·6	6·0	8·1 *	61·0	4·7	5·9	8·0 *	55	11·2
4′-Bromo-	48·6	3·7	4·8	5·2	48·5	3·7	4·7	5·4	35	5·7
4′-Chloro-	57·0	4·3	5·4	6·2	57·0	4·4	5·6	6·3	15	2·9

* Values for F (not S).

These results indicate that all four halogeno-derivatives should prove useful reagents for the precipitation of sulphate. However, the salts formed by the iodo-base with all the common acids were too insoluble to enable them to be used as reagents and this substance was not examined further. The sensitivity of the other three bases towards the sulphate ion decreased in the order of increasing sulphate solubility: that of the chloro-substituted base was comparable with that of barium chloride. The hydrochloride of 4-amino-4′-chlorodiphenyl is the most soluble of the halogeno-amines (*ca.* 0·35%), and as this amine also has the best sulphate-precipitating properties, it alone was examined as a possible reagent.

Preliminary experiments had shown that a boiling, saturated, aqueous solution of 4-amino-4′-chlorodiphenyl was alkaline towards phenolphthalein. Samples of its sulphate, freshly precipitated and also after various periods of storage, were readily titrated with alkali although the end-points with phenolphthalein were difficult to discern. Accordingly, a mixed indicator having a lower pH range was used in all subsequent titrations. Actual sulphate determinations were carried out to determine the most suitable conditions for precipitation. It was found that between pH 1 and 2 a two-fold excess of reagent and a standing time of 15—20 minutes gave quantitative recoveries of sulphate. Below pH 1, the hydrochloride of the base tended to be precipitated, and could not readily be washed out of the sulphate. Above pH 2, the precipitate was very finely divided and filtered slowly. It was difficult to dissolve the requisite amount of reagent in solutions of such acidity. Amounts of sulphate of 2·5—25 mg. and 25—100 mg. were rapidly and accurately determined under these conditions, a more concentrated reagent solution being used for the larger amounts of sulphate. Results are given in the following table.

Recoveries from pure sulphate solutions at pH 1·3—1·5.

SO_4^{2-} taken (mg.)	0·04775N-NaOH reqd., ml.	Vol. of 0·2% reagent (ml.)	SO_4^{2-} found (mg.)	SO_4^{2-} taken (mg.)	0·1256N-NaOH reqd., ml.	Vol. of 0·4% reagent (ml.)	SO_4^{2-} found (mg.)
2·53	1·10	20	2·53	25·33	4·20	80	25·31
5·07	2·21	30	5·08	38·00	6·30	120	37·94
10·15	4·42	60	10·15	50·66	8·41	160	50·62
10·47	4·52	75	10·47	63·33	10·52	200	63·33
15·20	6·61	90	15·17	75·99	12·62	240	75·99
20·26	8·82	120	20·25	88·66	14·71	280	88·55
22·91	9·98	150	22·88	101·32	16·82	320	101·30
25·33	11·03	150	25·32				

The effect of foreign ions on the recovery of 25 mg. of sulphate was examined. Of the common anions, chloride, bromide, iodide, nitrate, acetate, citrate, and tartrate did not interfere when present in 20-fold amounts (the maximum examined). Oxidising agents

except hydrogen peroxide interfered by decomposing the reagent; 5 ml. of 30% peroxide had no effect on the sulphate recovery. Zinc, copper, and magnesium formed soluble complexes with the reagent, but the results were not impaired when these elements were present in 10-fold amounts. Iron(III), chromium(III), calcium, and the alkali metals did not interfere when present in 20-fold amounts (the maximum examined). Aluminium seriously interfered by forming an insoluble complex salt containing neutral sulphate, but this was avoided by use of tartaric acid. Phosphate, tellurite, selenate, and oxalate interfered by forming insoluble salts with the reagent. Interference by phosphate was the only disadvantage in the use of this reagent, but this could be eliminated by prior removal as calcium phosphate or, with zinc oxide, as zinc phosphate.

Experimental

A. *Preparation of 4-Amino-4′-halogenodiphenyls and Their Sulphates.*—(i) *4-Amino-4′-chlorodiphenyl.* 4-Chloro-4′-nitrodiphenyl (69 g.) (prepared in 65% yield by Turner and Le Fèvre's method, *J.*, 1928, 253) was reduced with pure electrolytic iron and hydrochloric acid in 90% ethanol (cf. Gray, Hartley, and Jones, *J.*, 1952, 1959). Pure 4-amino-4′-chlorodiphenyl was obtained in colourless (or faintly yellow) shimmering plates on recrystallisation from light petroleum (b. p. 80—100°) (yield 95%; m. p. 128°, unchanged by vacuum-sublimation).

(ii) *4-Amino-4′-bromodiphenyl.* 4-Bromo-4′-nitrodiphenyl, obtained in 60—65% yield by Turner and Le Fèvre's method (*J.*, 1926, 2045), was reduced as for (i). Pure 4-amino-4-bromodiphenyl was obtained in pale yellow plates (yield 95%), m. p. 146°, unchanged by vacuum-sublimation.

(iii) *4-Amino-4′-iododiphenyl.* 4 : 4′-Dinitrodiphenyl (10 g.) was suspended in 50% ethanol (600 ml.) with vigorous stirring, and the mixture boiled under reflux. A solution of sodium sulphide nonahydrate (16 g.) and sulphur (4·2 g.) in water (60 ml.) was added during 15 min., and the mixture refluxed for a further ½ hr. After cooling, 4-amino-4′-nitrodiphenyl was filtered off and recrystallised from acetone; this gave 8 g. (90%) of orange-red, shimmering plates, m. p. 198°. This base (8 g.) was dissolved in glacial acetic acid (50 ml.), and the solution cooled to 10°. Solid sodium nitrate (2·5 g.) was gradually added (10 min.) to the vigorously stirred solution, which was then stirred for a further 15 min. The diazonium solution was decomposed with potassium iodide (4 g.) in water (15 ml.) and warmed on a water-bath until evolution of nitrogen had ceased. The mixture was diluted with water (250 ml.), and sulphur dioxide passed in for 1—2 min. The precipitated 4-iodo-4′-nitrodiphenyl was filtered off, washed well with water, and recrystallised from glacial acetic acid, giving 11 g. of yellow-brown needles, m. p. 204° (cf. Angeletti, *Giorn. Farm. Chim.*, 1926, **75**, 261). 4-Iodo-4′-nitrodiphenyl (10 g.) was refluxed with ethanol (100 ml.) containing concentrated hydrochloric acid (5 ml.); zinc dust (8·5 g.) was added in small portions (10 min.), and the solution refluxed for a further ½ hr., then filtered, and the ethanol removed by distillation. The residue was made alkaline and extracted by ether. The extract was evaporated, and the residual pale yellow solid recrystallised from light petroleum (b. p. 80—100°), giving pale yellow plates (6 g.), m. p. 165°.

(iv) *4-Amino-4′-fluorodiphenyl.* 4-Fluorodiphenyl was prepared by a modification of Schiemann and Roselius's method (*Ber.*, 1929, **62**, 1805). Diphenyl-4-diazonium chloride was treated with a solution of sodium borofluoride (cf. Adams, "Organic Reactions," 1949, Vol. V, p. 193). A quantitative yield of diphenyl-4-diazonium borofluoride was obtained, which was readily decomposed to give 4-fluorodiphenyl in 95% yield (cf. *op. cit.*). 4-Fluorodiphenyl (20 g.) was nitrated, and the 4-fluoro-4′-nitrodiphenyl reduced with zinc dust and hydrochloric acid (Van Hove, *loc. cit.*, p. 219). 4-Amino-4′-fluorodiphenyl was obtained as colourless plates from light petroleum (b. p. 80—100°) (yield 15 g.; m. p. 120°).

(v) *Preparation of sulphates.* 5 G. of each base were dissolved in sufficient 50% aqueous acetone and a solution of sulphuric acid in acetone was added until precipitation was complete. The sulphates were filtered off, washed with ether, and dried.

B. *Determination of Sulphate Solubilities.*—Belcher and Nutten's procedure (*loc. cit.*) was used.

C. *Determination of Sulphate.—Solutions required.* 4-Amino-4′-chlorodiphenyl hydrochloride, 0·24 and 0·48%* in 0·05N-hydrochloric acid. These solutions were prepared by dissolving with warming 2·4 g. and 4·8 g., respectively, of the hydrochloride in *ca.* 800 ml. of distilled water containing 50 ml. of N-hydrochloric acid. The solutions were filtered hot and diluted to

* Approximately equivalent to 0·2 and 0·4% solutions of free base.

1 l. On storage, the stronger solution precipitated some hydrochloride; accordingly, warm freshly prepared reagent was used.

Sodium sulphate, 0·052M. Approx. 7·34 g. of anhydrous sodium sulphate were dissolved in distilled water and the solution diluted to 1 l. This solution, containing approx. 5 mg. of SO_4^{2-} per ml., was standardised gravimetrically.

Sodium hydroxide, 0·1 and 0·05N.

Mixed indicator solution. 0·04% Aqueous phenol-red (sodium salt) and 0·04% aqueous bromothymol-blue (sodium salt), 3 : 2 by vol.

Procedure. (a) 2·5—25 Mg. of SO_4^{2-}. The sulphate solution (1—10 ml., pH 1—7) contained in a conical beaker was treated with a small amount of filter-paper slurry and sufficient tartaric acid was added to form a complex with any aluminium present (5 mg. of tartaric acid/1 mg. of Al). Sufficient 0·24% reagent solution was added to give a 2-fold excess (6 ml./1 mg. of SO_4^{2-}), and the mixture set aside for 15—20 min. (The acidity of the reagent ensured a final pH of 1—2 for precipitation.)

(b) 25—100 Mg. of SO_4^{2-}. This was effected as in (a), but with 5—25 ml. of sulphate solution, sufficient warm (40°) 0·48% reagent solution (3 ml./1 mg. of SO_4^{2-}), and 30 min. storage.

The subsequent procedure was identical for (a) and (b). The precipitate was filtered on a pulp filter, prepared as follows. A conical glass filter-funnel (diam. 3″) was three-quarters filled with water, the end of the stem being closed with one finger. A Witt plate (diam. 1″) was securely placed in the funnel, care being taken to remove any air bubbles trapped beneath it. A slurry of Whatman No. 41 filter-paper fibre was added, and the liquid allowed to drain from the stem. The layer of pulp (about ½″ deep) was gently and evenly pressed down, and the finger was replaced on the end of the stem. More slurry was added until, on draining, an amount equal to, or slightly less than that in the first layer, was obtained. The surface of the pad was gently tamped down, and the filter and pad washed with water. An unbroken column of water extended from the base of the plate to the end of the stem.

When all the precipitate had been filtered off, 5—10 ml. of the mother-liquor were returned to the precipitation vessel and used to transfer any appreciable amounts of precipitate which might have remained on the walls. The vessel was then washed well with two or three 5-ml. amounts of distilled water, the filter being allowed to drain before each addition of wash liquid. The precipitate was then washed with distilled water until the washings were chloride-free, and the filter drained under gentle suction. The upper layer of pulp was removed by a stainless-steel spatula and transferred to the precipitation vessel. The lower layer was used to transfer particles of precipitate adhering to the wall of the funnel.

The pulp slurry was then vigorously stirred to break up aggregates of precipitate. (This is essential for rapid and accurate titrations, because the sodium hydroxide reacts very slowly with the precipitate unless it is finely divided.) The filter-funnel was then washed with distilled water directly into the vessel. The contents of the vessel (40—50 ml.) were boiled for 1 min., 3 or 4 drops of indicator added, and the solution titrated with standard alkali (0·05N for 2·5—25 mg., 0·1N for 25—100 mg. of SO_4^{2-}) to the first purple colour in the solution. The solution was then re-heated, and the titration continued until the first permanent purple tinge was obtained. (The pulp retains a small amount of precipitate and the first end-point is false, although it is an excellent guide to the nearness of the true end-point.)

Recovery of reagent. When about 5 l. of filtration and titration liquors had accumulated, they were made alkaline and filtered on a Buchner funnel. The pulp residue was washed well with water, drained, and transferred to a 600-ml. beaker. The pulp was stirred with warm methanol (150 ml.), filtered, and washed with ether (200—300 ml.) in several portions. The ether and about 50 ml. of methanol were removed by distillation, and the distillate was retained for future recoveries of reagent. The methanolic solution of 4-amino-4′-chlorodiphenyl was treated with 50 ml. of 6N-hydrochloric acid, and the precipitated hydrochloride was dissolved by boiling, more methanol being added if necessary. On cooling, the hydrochloride crystallised in colourless leaves which were filtered off and dried. A further yield was obtained by concentrating the filtrate. The recovery of the reagent was almost quantitative.

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275. *The Quantitative Analysis of Inorganic Compounds by Paper Chromatography.*

By F. H. Pollard, J. F. W. McOmie, H. M. Stevens, and J. G. Maddock.

The use of paper chromatography in quantitative analysis is described for the determinations of (A) molybdenum and (B) copper and iron. A simple extraction process from the chromatogram is used to obtain solutions of the separated cations, which are then determined colorimetrically.

The separation of certain cations by chromatography on cellulose, and their subsequent determination by suitable means, have already been reported (*e.g.*, Lewis and Griffiths, *Analyst*, 1951, **76**, 388; Burstall and Wells, *ibid.*, p. 396; Kember and Wells, *ibid.*, p. 579; Lacourt *et al.*, *Mikrochem. Mikrochim. Acta*, 1949, **34**, 215, and later papers; Anderson and Lederer, *Analyt. Chim. Acta*, 1950, **4**, 513).

The cation to be determined in a mixture should have an R_F value differing from that of the others present by about 0·2. As described in this paper, Mo is completely separated from Co, Cr, Cu, Fe, Mn, Ni, U, and V by a mobile phase consisting of *n*-butanol saturated with a mixture of equal volumes of 2N-hydrochloric and 2N-nitric acid and containing 0·5% of benzoylacetone. The presence of the diketone improved the concentration and separation of the molybdenum spot, but it was omitted in the estimation since its presence affected the colorimetric determination. For copper and iron, the benzoylacetone was retained in the mobile phase, and its metal complexes were used for the colorimetric estimation.

Experimental

(A) *Determination of Molybdenum.*—The molybdenum was separated on a paper chromatogram from other cations and extracted from the excised paper with distilled water, and the extract estimated colorimetrically on a Hilger Spekker Photoelectric Absorptiometer, the colour produced with stannous–thiocyanate reagent being used.

(a) *Preparation of standard solutions and calibration of the absorptiometer.* A small quantity of "AnalaR" molybdenum trioxide was heated in a dish, and cooled in a desiccator. 1·8750 g. were dissolved in a minimum of hot sodium hydroxide solution, cooled, acidified with a few drops of 10N-hydrochloric acid, and diluted to 100 ml. with distilled water. This solution then contained 12·5 mg. of molybdenum per ml., and standard solutions (0·0125—0·0250 mg./ml.) were prepared from it by dilution by means of an Agla micrometer syringe fitted with a glass nozzle for the measurements of small volumes. To 4 ml. of each solution 1 ml. of the stannous–thiocyanate reagent (see below) was added, the mixture then being transferred to a 0·5-cm. glass cell. Readings on the Spekker drum were taken, Ilford No. 603 blue-green filters being used since a spectrophotometric examination of the solution indicated that absorption was strongest at 490 mμ. A calibration curve for these standard solutions was drawn, and used for subsequent determinations.

Stannous–thiocyanate reagent. Stannous chloride (2 g.) was heated with 10N-hydrochloric acid (3 ml.) until a clear solution was obtained; potassium thiocyanate (3 g.) was dissolved in 15 ml. of distilled water, and the two cold solutions were mixed just before use, and filtered.

(b) *Dissolution of the sample to be analysed.* If the sample was a steel, 1 g. of it was dissolved in 8 ml. of aqua regia, and the solution evaporated nearly to dryness. The residue was dissolved in the minimum quantity of warm 2N-hydrochloric acid, and then diluted to 10 ml. with distilled water. It is important that the final solution should not be too acid, otherwise the separation of molybdenum from the cations mentioned is not complete.

If the molybdenum is present in the sample as oxide or molybdate, a small quantity should be heated with 2N-sodium hydroxide, and the solution then acidified with a small excess of 2N-hydrochloric acid and finally diluted to a convenient volume with distilled water.

(c) *Preparation of the chromatogram.* A sheet of Whatman No. 1 filter-paper was prepared as shown in the Figure. A known volume of the prepared solution of the sample (0·15—0·20 ml.) was then delivered in drops of about 0·01 ml. from a microsyringe along the line *BC*. One drop of the same solution was placed at *A* and another at *D*; these served to locate the positions

of the cations after the chromatogram had been run. The prepared sheet was then placed in the chromatographic tank, the mobile phase being *n*-butanol which had been shaken with a mixture of equal volumes of 2N-nitric and 2N-hydrochloric acid (see " Observations," p. 1340). A run of about 14" from the starting line, taking about 18 hours, gave very satisfactory results. The sheet of paper was removed, and dried in a current of warm air.

R_F values (to $\pm 0{\cdot}02$) of cations in the solvent mixture (*a*) without and (*b*) with 0·5% (w/v) of benzoylacetone were : Cr, (*a*) 0·08, (*b*) 0·08; Co, (*a*) 0·09, (*b*) 0·08; Cu, (*a*) 0·11, (*b*) 0·11; Mn, (*a*) 0·11, (*b*) 0·10; U, (*a*) 0·25, (*b*) 0·21; V, (*a*) 0·18, (*b*) 0·17; Fe^{3+}, (*a*) 0·14, (*b*) 0·21; Fe^{3+} (with Mo 1 : 1), (*a*) 0·11, (*b*) 0·16; Ni, (*a*) 0·08, (*b*) 0·07; Ni (with Mo 1 : 1), (*a*) 0·07, (*b*) 0·07; Mo, (*a*) 0·41, (*b*) 0·30; Mo (with Fe^{3+} 1 : 1), (*a*) 0·47, (*b*) 0·45.

A mixture of the cations Mo, Fe, and Ni from a solution of Ridsdale's Alloy Steel No. 60B (C, 0·34; Si, 0·25; P, 0·014; Mn, 0·64; Ni, 2·59; Cr, 0·75; Mo, 0·43%) being used in acid, the corresponding R_F values with a mobile phase containing no benzoylacetone and 0·5% of benzoylacetone respectively were Mo, (*a*) 0·51, (*b*) 0·62; Fe^{3+}, (*a*) 0·19, (*b*) 0·27; Ni, (*a*) 0·07, (*b*) 0·06, while Cr and Mn remained behind with the Fe and Ni. Thus with a mixture of iron and molybdenum in approximately equal amounts, the R_F value of the former decreases while that of the latter increases. Where there are relatively large amounts of iron present, as in the above

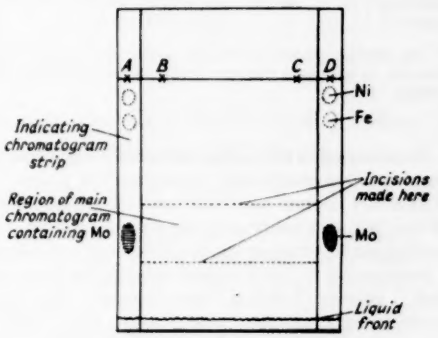

FIG. 1. *Chromatogram prepared from a Ni–Fe–Mo mixture.*

steel, the effect upon the R_F value of molybdenum is more pronounced. Other cations investigated seemed to have no appreciable effect.

If, in the preparation of the mobile phase, hydrochloric acid of concentration less than 2N was used, the molybdenum spot tended to " tail " a little, while with acid stronger than 2N, the iron spot moved towards the molybdenum spot until with 5N-acid there was practically no separation between them and considerable tailing. 2N-Nitric acid was included in the mobile phase to prevent the formation on the dried paper of " blue molybdenum oxide " which cannot be extracted by distilled water.

(d) *Extraction of molybdenum from the chromatogram.* The indicating chromatogram strips were then cut off and sprayed with the stannous–thiocyanate reagent which detects as little as 4×10^{-6} g. of molybdenum as an orange-pink spot. It was occasionally observed that a small blue ridge also appeared a few cm. below the orange spot, and this too was due to molybdenum (possibly owing to the reduction of the molybdenum complex to the " blue oxide " by the stannous ion). The indicating chromatogram strips were used to locate the molybdenum region on the main part of the sheet.

The main section of the chromatogram which contained the molybdenum was marked with pencil lines and warmed over an electric fire to drive off excess of acid and any traces of butanol held by the paper; two very light sprayings of ammonia solution (*d* 0·88) were applied to the marked portion, with intermediate and final drying. This treatment rendered the molybdenum section almost neutral, and it was then cut out, rolled up, tied with thread, inserted into a micro-Soxhlet apparatus, and refluxed with 20 ml. of distilled water for about 30 minutes. The extract was then concentrated to about 2 ml., centrifuged to remove any suspended matter, and diluted to 4 ml. with distilled water. To this the stannous–thiocyanate reagent (1 ml.) was then added, the mixture quickly transferred to a 0·5-cm. glass cell, and the reading determined in the absorptiometer. The concentration of the molybdenum was then read off from the calibration curve.

The following precautions were found to be necessary: (*a*) To avoid tight rolling of the excised strip, for this prevented complete extraction in 30 minutes; if necessary, the strip could be extracted in two portions. (*b*) To perform a "blank" test on a sheet of Whatman No. 1 filter-paper (treated exactly like a chromatogram and of the same dimensions). (*c*) To set the Spekker calibrated drum at a constant value of about 1·00 on the scale, distilled water being used in the 0·5-cm. cell, and the iris diaphragm control altered to obtain the initial null reading. (*d*) To use pieces of broken glass as boiling "chips" in the Soxhlet extraction apparatus, since porcelain introduces aluminium and iron.

It will be seen from the Table that the conditions for I(*c*) and II(*b*) give the most reliable results.

*Results obtained under different conditions.**

	Sample		pH of dry Mo strip before extraction	Mo, mg./ml. Found	Mo, mg./ml. Theor.
(I)	Standard Mo soln. containing Fe and Ni	(*a*)	1—2	0·032	0·022
		(*b*)	8—9	0·034	0·022
		(*c*)	6—7	(i) 0·022	0·022
				(ii) 0·180	0·176
(II)	Soln. of Ridsdale's Alloy 60B	(*a*)	6—7	(i) 0·035	0·025
				(ii) 0·029	0·025
		(*b*)	6—7	(i) 0·023	0·022
				(ii) 0·0256	0·0250

* The mobile phase in (II)(*a*) contained 0·5% (w/v) of benzoylacetone. The extracting solvent was water in all cases except (I)(*b*), in which it was 15 ml. of water plus 3 ml. of ammonia solution (*d* 0·880).

(B) *Determination of Copper and Iron.*—The two cations in the form of their benzoylacetone complexes can be completely separated on paper. The zones are separately extracted with alcohol and the copper and iron are determined with the Hilger Spekker Absorptiometer, an Ilford Filter No. 608 being used for copper and No. 604 for iron, as the benzoylacetone solutions show maximum absorption at the following wave-lengths: Cu 680—800 mμ, Fe 480 mμ.

(a) *Preparation of the standard solution and the calibration of the absorptiometer.* (i) Copper. "AnalaR" copper (2·500 g.) was dissolved in a small excess of nitric acid, and the solution evaporated to expel residual acid, cooled, and diluted to 25 ml. with distilled water. Measured volumes (0·01—0·12 ml.) of this standard solution were then separately diluted to 25 ml. with alcohol to which a few crystals of benzoylacetone had previously been added. The solutions were used to construct a calibration curve for copper, the 4-cm. cell being used.

(ii) Iron. Pure iron wire (0·125 g.) was dissolved in a small excess of nitric acid (*d* 1·220), and the solution diluted to 100 ml. with distilled water. A calibration curve for iron was then prepared in a manner similar to that for the copper except that one drop of nitric acid (*d* 1·42) was added to the solutions before dilution to 25 ml. with the alcoholic solution of benzoylacetone.

(b) *Preparation of chromatograms.* To test the accuracy of the method employed and the efficiency of the extraction process, chromatograms were prepared with measured volumes of standard solutions in a manner similar to that described for molybdenum. As the mobile phase, a solvent mixture consisting of *n*-butanol saturated with 0·5N-nitric acid, and containing 2% (w/v) of benzoylacetone was employed. The extraction of the excised portions containing copper and iron severally was carried out with alcohol in the micro-Soxhlet apparatus.

To each cold extract was added 1 drop of nitric acid (*d* 1·42), a few crystals of benzoylacetone, and then alcohol until the solutions were diluted to 25 ml. The copper and iron were estimated on the Spekker as described for the standard solutions, and the percentage recoveries calculated.

To correct for iron or copper impurities in the filter-paper itself, a blank sheet was treated exactly like a chromatogram. Portions similar in dimensions to those of the copper and iron were cut out and extracted, and the readings for the extracts obtained on the Spekker. A correction was then applied to the readings for the copper and iron determinations. "Blank" readings for the paper employed were of the following order (in terms of ml. of prepared standard solutions): copper, 0·001 ml. of standard Cu solution, equiv. to 0·0001 g. of Cu; iron, 0·01 ml. standard Fe solution, equiv. to 0·00001 g. of Fe.

Results.—In a series of experiments the following values for percentage recoveries of copper and iron were found after allowance for the "blank" correction:

Cu, 99·3, 98·9, 99·5, 99·5, 99·2, 98·9; mean = 99·2%. Fe, 99·1, 98·1, 99·6, 97·7; mean = 98·6%. Similar percentage recoveries were obtained on using a mixture of copper and iron.

Observations.—(1) A small excess of benzoylacetone added to the extracted cation solutions

was found to prevent loss of colour owing to dissociation. (2) As the benzoylacetone complexes of both metals under consideration are fairly highly coloured, their positions on the chromatogram can be determined quite well without the use of indicating strips. However, it is usually better to have such indicating chromatograms and to reveal the positions of the cations with as sensitive a reagent as possible. For copper, this would be rubeanic acid, and for iron, potassium thiocyanate.

(c) *Determination of copper and iron in brass.* B. C. S. Brass (1·5 g.) was dissolved in 7 ml. of nitric acid (*d* 1·42), and the excess of acid removed by boiling. The solution was then diluted to 10 ml. with distilled water. A chromatogram was prepared, as above, with 0·1 ml. of the prepared solution of the alloy. The copper and iron were determined exactly as in the experiments described above. A control experiment with standard copper and iron solutions was performed at the same time, as a further check. From the results of experiments performed in duplicate, the following values were obtained for the percentages of copper and iron in the brass (after allowance for the blank corrections): Cu, 57·7, 57·5 (mean = 57·6%), Fe 0·953, 0·957 (mean = 0·955%). After allowance for 99·2% and 98·6% recovery (see above), these values become 58·2 and 0·969%, respectively, the correct values being 58·2 and 0·95%.

THE UNIVERSITY, BRISTOL. [*Received, June 18th*, 1952.]

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276. *Molecular-orbital Calculations for Clar's Hydrocarbon 1 : 13 : 12-6 : 16 : 7-Dibenzonaphthacene (Zethrene).*

By C. A. COULSON and CARL M. MOSER.

The carbon–carbon bond lengths of the polynuclear hydrocarbon 1 : 13 : 12-6 : 16 : 7-dibenzonaphthacene ($C_{24}H_{14}$; Clar's zethrene) have been calculated by the simple molecular-orbital method. There is some evidence that the electronic structure differs from that of other polynuclear hydrocarbons with six-membered rings (*e.g.*, naphthalene, ovalene) on account of a low-lying π-electron orbital. It is suggested that the reduction of zethrene should lead first to a dihydrozethrene with a resonating framework related to that of 1 : 1-dinaphthylethylene, despite the fact that Clar's experiments with zinc dust or dithionite do not appear to confirm this. Further reduction, which leads experimentally to a chrysene derivative, can be interpreted by a plausible theoretical scheme. Calculations are also made of the expected ultra-violet transitions among π-electron levels, and a tentative interpretation is suggested for the three lowest energy bands.

RECENTLY Clar reported to us the synthesis of the hydrocarbon 1 : 13 : 12-6 : 16 : 7-dibenzonaphthacene $C_{24}H_{14}$ (I), which has been called zethrene from its **Z**-like structure. This hydrocarbon appears to have some properties that are rather unusual for polynuclear hydrocarbons.

The extremely close agreement between the bond lengths predicted by the simple molecular-orbital method for the polynuclear hydrocarbons ovalene (Buzeman, *Proc. Phys. Soc.*, 1950, *A*, **63**, 827) and coronene and pyrene (Moffitt and Coulson, *ibid.*, 1948, **60**, 309) and the bond lengths determined from the *X*-ray work of Robertson and his group made it of interest to ascertain whether such close agreement would also be found for zethrene. The determination of the bond lengths of zethrene is at present under investigation in the laboratories of Professor J. M. Robertson. For that reason it seems wise now to record the results of our calculations.

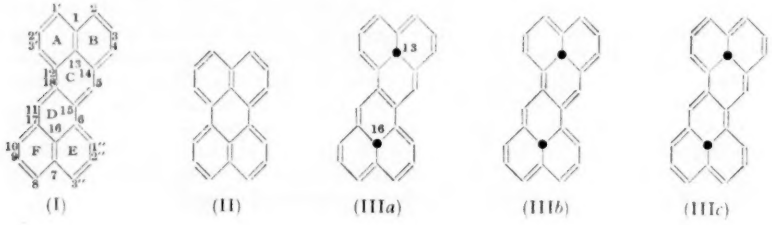
In addition to the calculations of the bond lengths, it seemed possible that the theoretical calculations might throw light on some of the unusual properties of this molecule.

In this paper we shall be concerned with: (1) a brief résumé of some of the properties of zethrene; (2) simple molecular-orbital calculations on the hydrocarbon; (3) bond

lengths and free valences determined from these calculations; (4) the electronic structure of the first excited states of zethrene and a comparison with the observed spectra; (5) a consideration of the successive reduction products of zethrene. In a later paper we hope to discuss the Diels–Alder reaction of zethrene with maleic anhydride.

Properties of Zethrene.—A complete report on the chemistry of zethrene will be given elsewhere by Clar and his collaborators. But it will be desirable to present here a brief résumé of some of its unusual properties. In the first place, if the bond diagram of the molecule is written in the usual way, there are nine Kekulé structures of which (I) is an example. This is because the molecule could be thought of as two naphthalene nuclei A–B and E–F conjugated together across a central butadiene-like region, 5, 15, 18, 11. Each naphthalene nucleus possesses three such structures, and those associated with rings A–B are independent of those associated with E–F. But in all nine structures the central region preserves a butadiene-like character. In excited structures, of course, this fixation of the central bonds ceases to hold. Yet we may expect, by analogy with other molecules, that the main features presented by the Kekulé diagrams will be found in the complete molecular diagram. A somewhat similar situation occurs in perylene (II), where the two bonds joining the naphthalene nuclei always appear as single bonds in the nine Kekulé structures which may be drawn analogous to those of (I). The longer length of these " single " bonds in perylene has now been established experimentally. It will be interesting to see whether a similar disparity is (*a*) predicted and (*b*) observed for zethrene.

Despite the nine Kekulé structures such as (I), Clar feels that the unusual properties of zethrene are best expressed, not by (I), but by a classical equilibrium between molecules of types (I) and (III). In (III) the periphery of the carbon skeleton has a normal aromatic character, and encloses two localised π-electrons on carbon atoms 13 and 16. It is a little difficult to see any satisfactory wave-mechanical justification for this localisation. If we accept it, there are three Kekulé structures (III*a*, *b*, *c*) which can be drawn. We shall discuss this matter, and also two further ways in which the π-electron distribution may differ from that to be expected on conventional grounds.

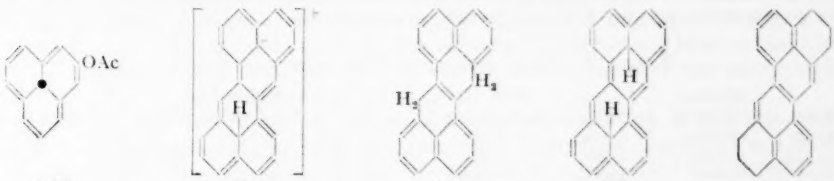


(I) (II) (III*a*) (III*b*) (III*c*)

Zethrene is green and its visible and its ultra-violet spectrum exhibit no relation to any class of aromatic hydrocarbons previously examined. This is surprising, since as Clar has shown, there are very striking regularities among the ultra-violet spectra of almost all other polynuclear aromatic hydrocarbons. Zethrene is sparingly soluble in neutral solvents but is readily soluble in dilute acetic acid. The spectrum of the neutral solution of zethrene differs considerably from that of the hydrocarbon in acid solvents and in some respects is similar to the spectrum of the free radical acetoxyperinaphthenyl (IV). The structure of zethrene in acid is considered by Clar to be (V). Reduction of the violet acid solution with zinc dust or hydrosulphite (dithionite) yields a yellow compound which Clar believes to be (VII), and which is readily re-oxidised to zethrene by oxygen. The possible dihydrozethrene (VII) differs from (VI), which was obtained by an independent synthesis, though when sublimed from the solid state, or when boiled with acetic acid, (VII) appears to be converted into (VI). Further reduction of (VI) with hydrogen iodide leads to a hydrocarbon (VIII), identified by means of its ultra-violet spectrum as a derivative of chrysene.

Molecular-orbital Calculations.—The usual molecular-orbital calculations have been

carried out for zethrene. Since they follow lines similar to those already published (*loc. cit.*) for coronene and ovalene, they will not be described in detail. The chief difficulty arises from the fact that since the only effective symmetry is that due to inversion in the centre of the molecule, the secular determinant cannot be reduced below two twelfth-order factors. The expansion of these was checked by using two distinct methods of building up the complete determinant out of smaller groups of atoms.



(IV) (V) (VI) (VII) (VIII)

The roots of the secular equation give the energies of the various molecular orbitals, and the values for zethrene are listed in Table 1. The roots listed in the $k(\beta)$ column are the energies found with the simplest approximation, that is when overlap between adjacent atomic orbitals is neglected. The energies (following Coulson, *Proc. Phys. Soc.*, **1948**, **60**, 257) are of the form :

$$E = E_0 + k\beta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where E_0 is the energy of the $2p_z$ electron on any nucleus (for zethrene the z direction is taken to be perpendicular to the plane of the molecule), β is the resonance integral, and k

TABLE 1. *Energies of molecular orbitals of zethrene.*

Symmetry *	$k(\beta)$	$m(\gamma)$		Symmetry *	$k(\beta)$	$m(\gamma)$	
A	−2·590	−7·351		A	0·199	0·189	
S	−2·359	−5·748		S	0·776	0·650	
A	−1·901	−3·621		A	1	0·8	
S	−1·808	−3·299		S	1	0·8	
A	−1·683	−2·905		S	1	0·8	
S	−1·421	−2·204	Antibonding	A	1·163	0·901	Bonding
S	−1·163	−1·640		A	1·421	1·049	orbitals
S	−1	−1·333		S	1·683	1·185	
A	−1	−1·333		A	1·808	1·245	
A	−1	−1·333		S	1·901	1·288	
A	−0·776	−0·962		A	2·359	1·484	
S	−0·199	−0·209		S	2·590	1·572	

* The wave functions symmetrical about the centre of symmetry are labelled S, those anti-symmetrical about the centre of symmetry are labelled A. Correct group-theory designations are S = a_u, A = b_g.

is the numerical coefficient for each energy level found from the secular determinant. As Wheland (*J. Amer. Chem. Soc.*, **1941**, **63**, 2025) has shown, the previously neglected overlap can easily be taken into consideration at this stage of the calculations. The energies of the orbitals (with overlap included) are now given by the equation :

$$E = E_0 + m\gamma \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where E_0 has its former meaning, $m = k/(1 + kS)$, $\gamma = \beta - S\alpha$, and $S = \int \phi_i \phi_j d\tau$ (i and j are neighbouring atoms). Where necessary S is given the numerical value of 0·25.

When the roots of the secular equation have been found, the coefficients for each atomic orbital in any molecular orbital can be readily determined (a list of these coefficients may be obtained on application to Dr. C. Moser). The molecular symmetry previously described compels the sets of coefficients to fall into two groups. In the first, called S, the coefficients for corresponding atoms (*e.g.*, 1 : 7 or 2 : 8) are equal : in the second, called A, they are equal and opposite. Full group-theory designations are a_u and b_g respectively.

Once the coefficients of the molecular orbitals have been obtained, the bond orders p follow very quickly (Coulson, *Proc. Roy. Soc.*, **1939**, *A*, **169**, 413). These mobile bond orders may be converted into bond lengths by the standard formula

$$x = s - \frac{s - d}{1 + K(1 - p)/p}$$

where s, d, x are the lengths, in Å, of a single bond, a double bond, and a bond of mobile order p, respectively, and K is a constant chosen so that the order–length curve passes

TABLE 2. *Bond orders and bond lengths in zethrene.*

Bond	Mobile bond order	Length (Å)	Length (Å) *	Bond	Mobile bond order	Length (Å)	Length (Å) *
1—2	0·550	1·416	1·416	12—13	0·540	1·418	1·417
1—13	0·527	1·420	1·420	12—18	0·425	1·440	1·437
1—1′	0·553	1·415	1·415	12—3′	0·628	1·401	1·411
2—3	0·694	1·388	1·396	13—14	0·510	1·423	1·425
3—4	0·645	1·398	1·391	15—18	0·466	1·432	1·411
4—14	0·601	1·406	1·420	1′—2′	0·701	1·389	1·393
5—14	0·513	1·422	1·408	2′—3′	0·637	1·400	1·394
5—15	0·692	1·390	1·412				

* These columns refer to a possible effect of configuration interaction. See p. 1345.

through the triple-bond point. This makes $K = 2(d - t)/(s - t)$, where t is the triple-bond length. The corresponding orders and lengths are shown in Table 2, columns 2, 3, 6, and 7. The basic lengths s, d, t have been taken equal to 1·540, 1·340, and 1·204 Å respectively. In view of our continuing ignorance of the true value of the double-bond length d, no absolute accuracy is expected for the third decimal in this table. But, as the example of ovalene suggests, relative validity may be much greater.

Since this molecule is an alternant hydrocarbon (Coulson and Longuet-Higgins, *ibid.*, 1947, *A*, **191**, 39), the charge distribution is uniform, to the approximation to which the method can be applied. But the free valences are not all equal (Burkitt, Coulson, and Longuet-Higgins, *Trans. Faraday Soc.*, 1951, **47**, 553). The free valence F_r at atom r is calculated from the formulæ

$$F_r = 1{\cdot}414 - \sum_s p_{rs} \text{ if } r \text{ is a secondary carbon atom}$$

$$F_r = 1{\cdot}732 - \sum_s p_{rs} \text{ if } r \text{ is a tertiary carbon atom}$$

Table 3 shows the values of F_r so obtained.

Bond Lengths and Free Valency.—The bond lengths reported in Table 2 suggest that the bonds most nearly double are those shown in (IX). The remaining bonds are all either (*a*) approximately equal to the normal aromatic length 1·39 Å, or (*b*) quite distinctly " single " in character. The bonds of type (*a*) are the remaining ones in the naphthalene nuclei, those of type (*b*) are the central ones. This means that the central part of the molecule resembles a butadiene system, as suggested above on the basis of Kekulé structures. We could say that there was a considerable degree of bond localisation in this region. The remaining " double " bonds in (IX) are the familiar 1 : 2-bonds of naphthalene. This shows, as is quite reasonable, that so far as possible, the naphthalene nuclei are not much distorted except where they are attached to the central " butadiene " system.

(IX)

As regards the free valence values, which would be expected to be significant in radical reactions, the most interesting figures are the high values at the atoms 5 and 11 which terminate the " butadiene " region, and the low values at the β-naphthalene positions 2′ and 3. The significance of the high values at 5 and 11 will be brought out in our discussion of dihydrozethrene.

The value of F_{13} is of some importance since it allows us to discuss Clar's suggestion that zethrene should be represented as (III) as well as (I). If (III) were a completely adequate description, then (1) the bond orders in the whole of the perimeter should be more

or less equal, and (2) the free valence at carbon atom 13 would be large. The first of these is certainly not the case, as we have seen (and we may hope for further verification of this when the experimental *X*-ray values for the bond lengths are available). The second is also not in accord with our calculations, which show that the free valence is effectively the same at positions 13 and 15 and not much greater than at position 12. This makes us feel that (III) is not a good representation of the electronic structure.

There is a further bond structure that might be considered as an alternative to (III). This is the lowest triplet state, in which there are two unpaired π-electrons. It differs from (III) in that in (III) the unpaired electrons are supposed to be strictly localised on atoms 13 and 16, whereas in the triplet state they will be distributed over the whole carbon skeleton. We shall consider this possibility in detail later.

The unusual properties of the ultra-violet spectrum and reduction of zethrene lead us to look for some unusual property of its energy levels. There is one such. It will be seen from Table 1 that the top occupied level has energy $E = E_0 + k\beta$, where $k = 0{\cdot}199$. This is exceedingly low, much lower, for example, than in benzene (1·000), naphthalene (0·618), or benzanthracene (0·452). It means that the energy difference between the lowest-energy configuration and the next higher one is only $2 \times 0{\cdot}199\beta = 0{\cdot}398\beta$. Three points follow from this. First on the assumption that the lowest configuration is indeed a good approximation to the true ground-state wave function, the excitation energy to the first excited state (an allowed transition, according to this view) would be much lower than usual. If such a low value is not found, it probably means that the lowest configuration is not a good enough approximation, and configuration interaction of the kind discussed by Coulson, Craig, and Jacobs (*Proc. Roy. Soc.*, 1951, *A*, **206**, 297) and by Coulson and Fischer (*Phil. Mag.*, 1949, **40**, 386) is more than usually important. This will have an effect on bond orders and bond lengths. Let us estimate it by making the rather extreme assumption that the two lowest configurations of similar symmetry (which correspond to configurations 1 and 4 in the article by Coulson and Fischer, *loc. cit.*) have equal weight. This almost certainly exaggerates the influence on bond lengths. The new bond lengths are shown in columns 4 and 8 of Table 2, under the heading of " configuration interaction." The most notable difference between columns 3 and 4 (and 7 and 8) lies in the smaller degree of bond fixation in columns 4 and 8, particularly in the " butadiene " region. Thus when the experimental lengths of the bonds are available, we may hope to have further information on this matter. Other changes than that of the bond 5–15 are within the reasonable precision of the whole scheme of calculation, according to Coulson, Daudel, and Robertson's analysis (*Proc. Roy. Soc.*, 1951, *A*, **207**, 306).

The second point which follows from the low value of k for the top occupied orbital is that the first excited triplet level, which arises from one electron each in the orbitals $k = +0{\cdot}199$, $k = -0{\cdot}199$, will be expected to have an unusually low energy. It is even conceivable that this energy might be as low as that of the lowest singlet state. In such an event, the molecule would behave very much as a diradical. It would be prohibitively difficult to make calculations *ab initio* to establish this situation. The present authors are inclined to believe that it would not happen. But it should mean that there was an unusually low-lying triplet state. Related to this would be the prediction that zethrene should show considerable thermal instability. We do not know of any evidence with regard to this.

The third point is that electrons in the two molecular orbitals for which $k = \pm 0{\cdot}199$ will behave in a manner rather similar to that of non-bonding electrons in zero-energy orbitals (Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 265). The actual values of the atomic coefficients in these molecular orbitals show that the electrons are almost entirely localised on atoms 1′, 3′, 2, 4, 5, and their mirror images in the centre of the molecule. The significance of this in any electronic interpretation of the reactivity of zethrene has been discussed fully by Longuet-Higgins. And the fact that this electron is hardly at all to be found on atom 13 is a further argument against the electronic bond diagram (III).

We can now discuss the possibility mentioned earlier that the quantum-mechanical version of Clar's concept of a classical equilibrium between two types of zethrene is not that of an equilibrium between (I) and (III), which we have seen to be theoretically

improbable, but that between (I) and the lowest triplet state. This could conceivably occur if the triplet energy was sufficiently low. But we believe that such an interpretation is not correct, for the following reasons. First, on account of the complementary character of the singly-occupied orbitals $k = \pm 0{\cdot}199$, in this triplet state the net distribution of π-electrons is the same as in the ground state. Second, the two most loosely bound electrons—the unpaired electrons of the triplet—have a distribution which, as stated earlier, is almost entirely localised on atoms 1′, 3′, 2, 4, 5, and their mirror images. Thus there would be nothing resembling free electrons on atoms 13 and 16 in the triplet state any more than in the singlet ground state. Thirdly, the free valence values, shown in Table 3,

TABLE 3. *Free valence* (F.V.) *in ground state and first-excited (triplet) state.*

Carbon nos.	1,7	2,8	3,9	4,10	5,11	6,12	13,16	14,17	15,18	1′,3″	2′,2″	3′,1″
F.V. (ground)	0·102	0·170	0·075	0·168	0·210	0·139	0·155	0·108	0·150	0·160	0·076	0·149
F.V. (triplet)	0·098	0·210	0·078	0·168	0·192	0·162	0·154	0·078	0·156	0·188	0·078	0·174

show that the values for atoms 13 and 16 in the triplet state scarcely differ from their values in the singlet ground state, so that the arguments used for the latter apply equally for the former. For these reasons it appears improbable that the concept of a classical equilibrium can be justified in terms of the triplet state. And there is no other state of sufficiently low energy.

It is worth while to refer briefly to the electronic transitions which our simple theory predicts. It is well known that on account of its failure to take adequate account of varying spin multiplicity these predictions must be accepted with considerable reserve. If we make use of the energies given in Table 1, then the three lowest energy transitions among the π-electrons are as shown in Table 4. Additional transitions at shorter wavelengths can soon be written down. We have not done so because they are close together, and their resulting absorption bands would certainly overlap. Now the visible and near ultra-violet spectrum of zethrene has been determined by Clar ("Aromatische Kohlenwasserstoffe," Springer, Berlin, 2nd edn., 1952, p. 389). There are weak maxima ($\log \varepsilon \sim 3$) at 622 and 573 mμ, followed by a strong band ($\log \varepsilon \sim 5$) at 461 mμ, and another fairly strong band ($\log \varepsilon \sim 4$) at 342 mμ. Whether or not we treat the two bands at 622 and

TABLE 4. $N \longrightarrow V$ *Transitions in zethrene.*

Transition	Description * of electron jump		Excitation energy (units of γ)	λ(mμ) †
$N \longrightarrow V_1$	$b_g \longrightarrow a_u$	Allowed	0·398	943
$N \longrightarrow V_2$	$a_u \longrightarrow a_u$	Forbidden	0·859	437
$N \longrightarrow V_3$	$b_g \longrightarrow a_u$	Allowed	1·009	372
$N \longrightarrow V_4$	$b_g \longrightarrow b_g$	Forbidden	1·151	326

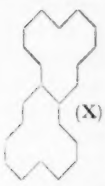
* With usual selection rules $u \longrightarrow g$ and $g \longrightarrow u$ transitions are allowed, $u \longrightarrow u$ and $g \longrightarrow g$ are forbidden, as with atomic spectra.

† Excitation energies are calculated with $\gamma = 3{\cdot}3$ ev.

523 mμ as corresponding to different vibrational quanta of one electronic transition (the difference is unusually large for this interpretation) there does not appear to be any way of correlating these with the predicted transitions, as given in Table 4. The only conclusion which we feel entitled to draw from this is that it provides further support for the tentative suggestion made earlier, that on account of the low-energy orbital, configuration interaction is more important for this molecule than for most others. If the first excited transition is correctly interpreted, there should be a triplet of much lower energy. So far as we know, no data are available with which to test this view.

Reduction of Zethrene.—We may now discuss the reduction of zethrene, which, according to Clar, is not to the expected (VI), but is rather to (VII). Free valence considerations would have suggested that (VI) was formed more readily than (VII), as we have already said. A similar conclusion is obtained on the basis of energy stability. To prove this, let us compare the loss of π-electron energy in the two processes: (1) (I $\longrightarrow$ VI); (2) (I $\longrightarrow$ VII).

The first of these processes leads to a resonating framework which, as regards its π-electron structure, can be regarded as almost equivalent to 1 : 1-dinaphthylethylene. The values of the energies of the molecular orbitals of this system are available (Berthier, Berthod, Mayot, and Pullman, *Compt. rend.*, **1950**, **231**, 1149), so that the total π-electron energy is soon found. The second process leads to a resonating framework which, as a first approximation, is shown in (X). For purposes of calculating the energies of the orbitals, this is equivalent to a cyclic polyene of 22 atoms, with a bond along one diameter. The method of calculating the energies is quite straightforward and will not be described here. When the sets of energies, for the two processes, are converted into the more accurate γ-values, the values of the total π-electron energies are found to be:



(X)

Zethrene	$24E_0 + 23{\cdot}935\gamma$
(IV)	$22E_0 + 21{\cdot}688\gamma$
(VII)	$22E_0 + 20{\cdot}338\gamma$

Thus, (VI) is more stable than (VII) by about $1{\cdot}35\gamma = 4{\cdot}4$ ev. This is so large that it appears unlikely from our calculations that (VII) would be actually obtained in practice. We are more inclined to believe the suggestion of Professor M. J. S. Dewar (personal communication which we are glad to acknowledge here), that the first, easily reversible, reduction product is a monohydro-compound stabilised by resonance rather like a semi-quinone, but which, in certain circumstances, may dismutate into the dihydro-compound (VI). This interpretation cannot, however, be regarded as proved.

We have still to explain the final reduction of zethrene to the chrysene derivative (VIII). At first sight one would have expected reduction of the 5 : 11-dihydro-compound (VI) to take place by addition of hydrogen atoms at the central "olefinic" bond, giving a tetrahydro-compound. Now formation of (VIII) involves migration of the two hydrogen atoms first added. It seems probable that this migration is to positions 2 and 8. There are two reasons for this. In the first place, as Table 3 shows, the free valence at positions 2 and 8 is large, and particularly so if the activated state resembles the triplet level, where the free valence is a maximum precisely at these positions. And in the second place it can be shown from a comparison of the various calculated resonance energies that the difference in energy between the 5 : 11- and 2 : 8-dihydro-compounds is only about 3 kcal./mole. It is almost certain that the 2 : 8-compound, if it existed at all, would easily be reduced to the observed chrysene derivative (VIII). According to this picture, the reduction of zethrene proceeds first to a monohydro-compound, then to the 5 : 11-dihydro-compound; this suffers hydrogen atom migration from positions 5 : 11 to 2 : 8, either accompanied or perhaps followed by the addition of two molecules of hydrogen to give (VIII). Without the intermediate migration to positions 2 : 8, it is not easy to see how the chrysene system could be formed, nor indeed how a total of three molecules of hydrogen can be added to the parent molecule. This complete mechanism, even if it is correct, does not distinguish between the possible singlet or triplet ground states. Presumably only magnetic susceptibility measurements could do this.

In conclusion we acknowledge most warmly the kindness of Dr. Clar in telling us about this new molecule before publication of his work, and for other helpful correspondence.

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277. *Synthesis of Diaminoxanthones.*

By A. A. Goldberg and H. A. Walker.

1 : 5-, 1 : 6-, 1 : 7-, 2 : 5-, 2 : 6-, 2 : 7-, 3 : 5-, and 3 : 6-Diaminoxanthone have been synthesised (for examination for activity against *M. tuberculosis*) by two routes: (i) cyclodehydration of *o*-phenoxybenzoic acids bearing a nitro- or acetamido-group in each nucleus, followed by reduction or deacetylation of the resulting dinitro- or bisacetamido-xanthone; and (ii) nitration of a nitroxanthone and reduction of the dinitroxanthone thus obtained.

The influence of electron-attracting and electron-repelling groups in the 3′-position on the direction of cyclisation of *o*-phenoxybenzoic acids has been investigated. 3′-Nitro-derivatives cyclise principally upon the 2′-position whereas with 3′-acetamido-derivatives ring closure takes place exclusively at the 6′-position.

Nitrating agents attack 1-, 2-, 3-, and 4-nitroxanthone at the same position, giving respectively 1 : 7-, 2 : 7-, 2 : 6- and 2 : 5-dinitroxanthone. Nitration of xanthone leads successively to 2-nitro-, 2 : 7-dinitro-, and 2 : 4 : 7-trinitroxanthone. It has been shown that "α-dinitroxanthone," described in the literature as "1 : 8-" and "2 : 4-"dinitroxanthone, is actually 2 : 4 : 7-trinitroxanthone.

During the search for functional derivatives and spatial analogues of 4-aminosalicylic acid active against *Mycobacterium tuberculosis* a number of amino- and diaminoxanthones has been prepared. 3-Amino- and 3 : 6-diamino-xanthone bear formal resemblance to 4-aminosalicylic acid and the antimycobacterial diphenyl ethers described by Barry (*Proc. Roy. Irish Acad.*, 1950, **53**, *B*, 55). It is of interest that various dialkylaminoalkyl derivatives of 1-aminoxanthone have of recent years attained chemotherapeutic value on account of their schistosomicidal properties (Mauss, *Chem. Ber.*, 1948, **81**, 19).

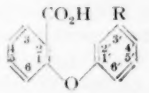
Of the ten theoretically possible heteronuclear diaminoxanthones only one—the 2 : 7-isomeride—is recorded in the literature. The present communication describes the synthesis of 1 : 5-, 1 : 6-, 1 : 7-, 2 : 5-, 2 : 6-, 2 : 7-, 3 : 5-, and 3 : 6-diaminoxanthone and new routes to 1- and 4-monoaminoxanthone.

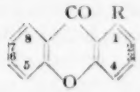
Two general methods have been employed for the preparation of the diaminoxanthones, *viz.*; (i) cyclodehydration of *o*-phenoxybenzoic acids bearing a nitro- or acetamido-substituent in each nucleus, followed by reduction or deacetylation of the resulting dinitro- or bisacetamido-xanthone; and (ii) nitration of a nitroxanthone and reduction of the dinitroxanthone thus obtained. The orientations have been established either by unequivocal synthesis or by establishing an identity between the products obtained by the two different synthetic routes each of which fixes the position of one substituent.

m-Nitrophenol condensed readily with the 3-, 4-, 5-, and 6-nitro-derivatives of *o*-chlorobenzoic acid, giving respectively 2-carboxy-6 : 3′-, -5 : 3′-, -4 : 3′-, and -3 : 3′-dinitrodiphenyl ether. These on reduction and acetylation yielded the bisacetamido-derivatives; the corresponding diamino-acids were too unstable for isolation in satisfactory yield. Both *o*- and *p*-nitrophenol, however, failed to condense with the nitro- and acetamido-derivatives of *o*-chlorobenzoic acid. This is apparently due to the weak anionoid properties of these phenols caused by lowering of electron availability on the phenolic oxygen atom by the *o*- or *p*-nitro-group. (Compare the reluctance of *o*- and *p*-nitroaniline, and the readiness of *m*-nitroaniline, to condense with *o*-chlorobenzoic acids: Bogert and Hirschfelder, *Coll. Trav. chim. Czeckoslov.*, 1930, **5**—**6**, 382; Albert and Linnell, *J.*, 1936, 1614; Goldberg and Kelly, *J.*, 1946, 102; Goldberg, *J.*, 1952, 4368.) *o*-*p*′-Nitrophenoxybenzoic acids may be easily obtained, however, by nitrating *o*-phenoxybenzoic acids (see below).

On the other hand, *o*- and *p*-acetamidophenol reacted smoothly with 2-chloro-5-nitrobenzoic acid to yield respectively 2′- and 4′-acetamido-2-carboxy-4-nitrodiphenyl ether which, on cyclisation and subsequent deacetylation, gave 5- and 7-amino-2-nitroxanthone; reduction of these yielded 2 : 5- and 2 : 7-diaminoxanthone. With 2-chloro-4-nitrobenzoic acid both *o*- and *p*-acetamidophenol at 120° in amyl alcohol effected reductive dehalogenation with production of *p*-nitrobenzoic acid in high yield (cf. the hydrogenolysis of the

2-chloro-group in 2-chloro-4-nitrobenzoic acid by *p*-phenylenediamine; Goldberg and Kelly, *loc. cit.*). 2-Chloro-3-nitrobenzoic acid condensed with *p*-hydroxyacetanilide to give 4′-acetamido-2-carboxy-6-nitrodiphenyl ether which by cyclisation, deacetylation, and reduction was converted into 2 : 5-diaminoxanthone. Reaction of 3-acetamido-2-chlorobenzoic acid with *o*- and *p*-acetamidophenol gave only 3-acetamidobenzoic acid.


(I)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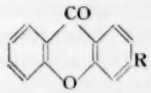
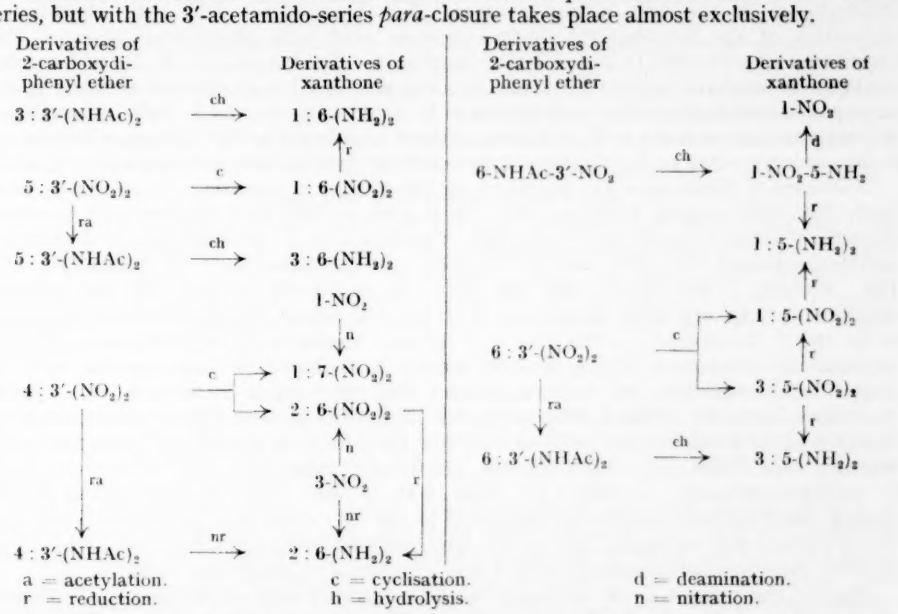

(III)

Cyclodehydration of Substituted o-*Phenoxybenzoic Acids.*—While 2′- and 4′-substituted *o*-phenoxybenzoic acids can undergo cyclodehydration with formation in each case of only one product, the 3′-substituted acids (I) may give 1- or 3-substituted xanthones according to whether ring closure proceeds upon the 2′- (II) (*ortho*-closure) or the 6′-position (III) (*para*-closure). There are no records of the influence of 3′-substituents in this reaction other than that by Dhar (*J.*, 1920, 1064) who obtained 1-nitroxanthone by cyclodehydration of *o*-*m*′-nitrophenoxybenzoic acid.

The present communication describes the cyclodehydration of a series of 3′-nitro- and 3′-acetamido-derivatives and in all cases *ortho*-closure predominates with the 3′-nitro-series, but with the 3′-acetamido-series *para*-closure takes place almost exclusively.



Thus 2-carboxy-4 : 3′-dinitrodiphenyl ether gave a product containing *ca.* 85% of 1 : 7- and *ca.* 15% of 2 : 6-dinitroxanthone. These were separable by their different solubilities in toluene and their structures established by their respective identities with the dinitroxanthones obtained by the nitration of 1- and 3-nitroxanthone (see scheme). Reduction with stannous chloride yielded 1 : 7- and 2 : 6-diaminoxanthone. Cyclodehydration of 4 : 3′-bisacetamido-2-carboxydiphenyl ether followed by hydrolysis yielded 2 : 6-diaminoxanthone as sole product.

Cyclisation of 2-carboxy-5 : 3′-dinitrodiphenyl ether gave a product which was apparently not completely homogeneous but from which only 1 : 6-dinitroxanthone could be isolated, the yield being of the order of 80%. This was reduced to 1 : 6-diaminoxanthone, the structure of which was proved by its identity with the diaminoxanthone obtained by cyclisation of 3 : 3′-bisacetamido-2-carboxydiphenyl ether followed by

hydrolysis. Cyclisation of 5 : 3′-bisacetamido-2-carboxydiphenyl ether acid yielded one product only which, being different from the foregoing 1 : 6-diaminoxanthone, must be 3 : 6-diaminoxanthone. Both 2-carboxy-3 : 3′-dinitro- and 3-acetamido-2-carboxy-3′-nitro-diphenyl ether resisted cyclisation with sulphuric acid or phosphoryl chloride or by Gottesmann's method (*Ber.*, 1933, **66**, 1168) (compare the inability 3-acetamido-2-carboxy-3′-nitrodiphenylamine to cyclise; Goldberg and Kelly, *J.*, 1947, 596).

Treatment of 2-carboxy-6 : 3′-dinitrodiphenyl ether with sulphuric acid gave a product separable by crystallisation from pyridine into the less soluble 1 : 5-dinitroxanthone, m. p. 304°, and the more soluble 3 : 5-isomer, m. p. 234°, in the ratio of *ca.* 80 : 20; reduction of these yielded 1 : 5- and 3 : 5-diaminoxanthone, m. p. 266° and 270° respectively. Cyclisation of 6 : 3′-bisacetamido-2-carboxydiphenyl ether and deacetylation of the product gave 3 : 5-diaminoxanthone, m. p. 270°, in quantitative yield, identical with the compound obtained by reduction of the more soluble dinitroxanthone. Authentic 1 : 5-diaminoxanthone was obtained by condensation of 3-acetamido-2-chlorobenzoic acid with *m*-nitrophenol to give 6-acetamido-2-carboxy-3′-nitrodiphenyl ether which on cyclodehydration yielded a compound which must be 5-amino-1-nitroxanthone, and not the 3 : 5-isomer, since on deamination it was converted into 1-nitroxanthone. Reduction of this 5-amino-1-nitroxanthone yielded 1 : 5-diaminoxanthone.

Nitration of Mononitroxanthones.—The mononitroxanthones were obtained by condensation of the four nitro-derivatives of *o*-chlorobenzoic acid with phenol and cyclisation of the resulting nitrophenoxybenzoic acid with phosphoryl chloride; this constitutes a novel route to 1- and 4-nitroxanthones. Treatment of 1-, 2-, 3-, and 4-nitroxanthone in sulphuric acid with 1·1 mol. of nitric acid in all cases effected nitration in the same position with production respectively of 1 : 7-, 2 : 7-, 2 : 6-, and 2 : 5-dinitroxanthone. A more expeditious route to 2 : 6-dinitroxanthone was found to be nitration of 2-carboxy-5-nitrodiphenyl ether and cyclisation of the resulting 5 : 4′-dinitro-acid with sulphuric acid.

Nitration of Xanthone.—The literature on this subject is confusing. Graebe (*Annalen*, 1889, **254**, 285) treated xanthone with nitric acid at 100° and obtained the benzene-insoluble " β-dinitroxanthone," m. p. 260°, together with a small amount of a benzene-soluble compound, m. p. 190°, which he termed " α-dinitroxanthone " (cf. Perkin, *J.*, 1883, 193; Richter, *J. pr. Chem.*, 1883, **28**, 273). Bayer (*Annalen*, 1910, **372**, 80) nitrated xanthone in sulphuric acid, obtaining a 90% yield of β-dinitroxanthone which he proved to be the 2 : 7-isomeride. Dhar (*loc. cit.*) nitrated xanthone in cold sulphuric acid and recorded the production of the alcohol-insoluble 2 : 7-dinitroxanthone together with an alcohol-soluble mixture of 3-nitroxanthone and unchanged xanthone. Das Gupta (*J. Indian Chem. Soc.*, 1932, **9**, 393) converted " α-dinitroxanthone " into a nitroxanthonyl-arsinic acid for which he gave, without evidence, the structural formula of 1-nitroxanthone-8-arsinic acid (*Chem. Abs.*, 1933, **27**, 498, accordingly referred to the " α "-compound as 1 : 8-dinitroxanthone). Le Fèvre (*J.*, 1937, 200) nitrated xanthone with excess of cold fuming nitric acid and obtained a high yield of the " α "-compound, m. p. 180—187° (for which carbon and hydrogen, but no nitrogen, analyses were recorded), and from dipole moment measurements concluded that it was " impure 2 : 4-dinitroxanthone."

During the present work xanthone has been nitrated with an excess of cold fuming nitric acid for 4 days by Le Fèvre's method. The product consisted of *ca.* 50% of the benzene-insoluble 2 : 7-dinitroxanthone and *ca.* 50% of the benzene-soluble " α "-compound, m. p. 180—186°, raised to 204° by crystallisation with little loss in yield. Reduction of the nitration time increased the yield of the 2 : 7-dinitroxanthone and decreased that of the " α "-compound. No other compounds could be isolated from the reaction product. The m. p. of the " α "-compound was considerably depressed by authentic 2 : 4-dinitroxanthone (m. p. 204°); analysis showed it to be, in fact, a trinitroxanthone. The production of the same substance both by mononitration of 2 : 7-dinitroxanthone and by dinitration of 4-nitroxanthone established its identity as 2 : 4 : 7-trinitroxanthone. The " α "-compound obtained in small yield by nitrating xanthone in cold sulphuric acid by Perkin's or Bayer's method has also been shown to be 2 : 4 : 7-trinitroxanthone. It appears that this is the substance obtained by Dhar (*loc. cit.*) by nitration of 2-nitroxanthone and termed by him 2 : 3 : 7-trinitroxanthone.

Nitration of xanthone in sulphuric acid solution with the theoretical amount of fuming nitric acid yielded principally 2-nitroxanthone. Small amounts of 2 : 7-dinitroxanthone together with unchanged xanthone, but no 3-nitroxanthone, could be isolated from the reaction product (cf. Dhar, *loc. cit.*).

It is accordingly apparent that the nitration of a nitroxanthone leads invariably to a heteronuclear dinitroxanthone and that the 2- and the 7-position in the xanthone molecule are the positions predominantly activated towards attack by nitrating agents. The 4- and the 5-position are reactive but less so than the 2- and the 7-position, as shown by the fact that there is little nitration at the 4(or 5)-position unless the 2- and the 7-position are already occupied.

Experimental

General Procedure for the Condensation of o-Chlorobenzoic acids with Phenols.—The condensation between an *o*-halogenobenzoic acid and a phenol takes place less readily than that between the former and an arylamine (cf. Goldberg and Kelly, *J.*, 1946, 104; Goldberg, *J.*, 1952, 4368); for the higher temperature needed, nitrobenzene, hexyl alcohol, and anisole are suitable solvents since these, being volatile in steam, are easily removed from the reaction mixture. In some cases no solvent is necessary. The *o*-chlorobenzoic acid was normally dissolved in *ca.* 4 times its weight of nitrobenzene, and the catalyst and potassium carbonate (1·0—1·5 mol.) were added portionwise to the solution stirred at *ca.* 80° in order to obtain the salt in a voluminous state. After addition of the requisite phenol, stirring was continued at the stated temperature; water formed during the reaction was allowed to distil off. The mixture was diluted with water, the solvent removed in steam, and the residual aqueous solution filtered from tar. Acidification to pH 6 often precipitated more tar; after removal of this, the filtrate was adjusted to pH 2 and the carboxydiphenyl ether collected. The most economical method of purification was found to be dissolution in water and *ca.* 3 mols. of potassium carbonate, evaporation to small volume, collection of the salt, and its reconversion into the free acid. In some cases purification *via* the calcium salt was more effective.

Series from 2-chloro-4-nitrobenzoic acid.

2-*Carboxy*-5 : 3′-*dinitrodiphenyl Ether*.—2-Chloro-4-nitrobenzoic acid (40·2 g., 0·2 mol.) was stirred with nitrobenzene (250 c.c.), anhydrous potassium carbonate (42 g., 0·3 mol.), copper bronze (1 g.), cuprous iodide (1 g.), and *m*-nitrophenol (31 g., 0·22 mol.) at 155° (internal) for 6 hours. The crude 2-*carboxy*-5 : 3′-*dinitrodiphenyl ether* (40 g.) had m. p. 176—180°; a sample crystallised from 60% alcohol in yellow needles, m. p. 188—190° (Found: *M*, 302; N, 9·4. $C_{13}H_8O_7N_2$ requires *M*, 304; N, 9·2%).

1 : 6-*Dinitroxanthone*.—A solution of the foregoing acid (50 g.) in concentrated sulphuric acid (300 c.c.) was heated on the water-bath for 1 hour and poured on powdered ice (3 kg.). Extraction of the precipitate with boiling 2½% sodium carbonate solution left a residue of crude 1 : 6-*dinitroxanthone* (47 g., m. p. 242°) which crystallised from dilute pyridine in fawn-coloured leaves, m. p. 250—252° (Found: C, 54·6; H, 2·2; N, 10·0. $C_{13}H_6O_6N_2$ requires C, 54·5; H, 2·1; N, 9·8%).

1 : 6-*Diaminoxanthone*.—Crude 1 : 6-dinitroxanthone (30 g.) was added during ¾ hour to a solution of stannous chloride dihydrate (300 g.) in 10N-hydrochloric acid (300 c.c.) stirred at 100°. Stirring was continued at this temperature for a further 2½ hours, the mixture kept in the refrigerator overnight, and the yellow magma drained at the pump on sintered glass. The solid was stirred for ½ hour with cold 5N-sodium hydroxide (1 l.), and the insoluble material collected, washed with cold water and dried; the yield of crude 1 : 6-*diaminoxanthone* was 17 g. (m. p. 240—250°). A sample crystallised from dilute pyridine in glittering yellow tablets, m. p. 254—256° alone and in admixture with the material prepared by cyclisation and deacetylation of 3 : 3′-bisacetamido-2-carboxydiphenyl ether (Found: C, 68·6; H, 4·3; N, 12·6. $C_{13}H_{10}O_2N_2$ requires C, 69·0; H, 4·4; N, 12·4%).

5 : 3′-*Bisacetamido*-2-*carboxydiphenyl Ether*.—A solution of 2-carboxy-5 : 3′-dinitrodiphenyl ether (50 g.) in aqueous ammonia (500 c.c.; *d* 0·880) was saturated with hydrogen sulphide, kept overnight, then heated at 80° for 4 hours during which hydrogen sulphide was passed in. The mixture was boiled to remove ammonia, filtered from sulphur, and chilled, and sodium carbonate (50 g.) and then acetic anhydride (40 c.c.) were added dropwise with stirring at 20°; after a further 2 hours' stirring at this temperature, the solution was acidified with 5N-hydrochloric acid and the precipitate collected. Recrystallisation from dilute alcohol gave 5 : 3′-*bisacetamido*-2-*carboxydiphenyl ether* (30 g.) in colourless nacreous plates, m. p. 274—276° (decomp.) (Found: *M*, 327; N, 8·7. $C_{17}H_{16}O_5N_2$ requires *M*, 328; N, 8·6%).

3 : 6-*Diaminoxanthone*.—The foregoing bisacetamido-acid (25 g.) was heated at 100° with concentrated sulphuric acid (150 c.c.) for 2 hours. The solution was cooled and, after the addition of water (40 c.c.), heated on the water-bath for ½ hour to effect deacetylation, and poured on crushed ice (1500 g.). The precipitate was extracted with dilute aqueous ammonia and crystallised from dilute pyridine; **3 : 6-*diaminoxanthone*** (12 g.) was obtained in lemon-coloured needles, m. p. 324—326° (Found : C, 68·8; H, 4·6; N, 12·5. $C_{13}H_{10}O_2N_2$ requires C, 69·0; H, 4·4; N, 12·4%).

Series from 2-chloro-5-nitrobenzoic acid.

2-*Carboxy*-4 : 3′-*dinitrodiphenyl Ether*.—2-Chloro-5-nitrobenzoic acid (65 g., 0·32 mol.), *m*-nitrophenol (46 g., 0·33 mol.), anhydrous potassium carbonate (42 g., 0·32 mol.), copper bronze (0·5 g.), and nitrobenzene (200 c.c.) were stirred together at 160° for 4½ hours. The crude **4 : 3′-*dinitro-acid*** (68 g.) had m. p. 200° and crystallised from 75% alcohol in prisms, m. p. 206° (Found : *M*, 306; N, 9·4. $C_{13}H_8O_7N_2$ requires *M*, 304; N, 9·2%).

1 : 7- *and* 2 : 6-*Dinitroxanthone*.—A solution of the foregoing acid (20 g.) in sulphuric acid (100 c.c.; *d* 1·84) was heated at 100° for 2 hours and poured on ice (500 g.). The precipitate was washed with dilute aqueous sodium carbonate and dried (yield, 17·5 g.; m. p. 235—250°). Extraction with boiling benzene (2 × 100 c.c.) left nearly pure **1 : 7-*dinitroxanthone*** (12·5 g.), m. p. 260°, which on crystallisation from toluene gave the pure compound in pale yellow plates, m. p. 264° alone and admixed with material prepared by mononitration of 1-nitroxanthone (Found : C, 54·5; H, 2·0; N, 9·9. $C_{13}H_6O_6N_2$ requires C, 54·5; H, 2·1; N, 9·8%). By a tedious fractional crystallisation from toluene of the material extracted by the benzene there was obtained 0·6 g. of **2 : 6-dinitroxanthone**, m. p. 268° (Found : N, 10·0%). This m. p. was strongly depressed by admixture with the foregoing 1 : 7-dinitroxanthone but not by 2 : 6-dinitroxanthone obtained by nitration of 3-nitroxanthone. The solubilities of 1 : 7- and 2 : 6-dinitroxanthone were too similar for easy separation of the latter; after reduction, however, the mixture of 1 : 7- and 2 : 6-diaminoxanthone was easily separable.

1 : 7- *and* 2 : 6-*Diaminoxanthone*.—The foregoing crude precipitate of 1 : 7- and 2 : 6-dinitroxanthones (14 g.) was added during ½ hour to a solution of hydrated stannous chloride (80 g.) in 10N-hydrochloric acid (80 c.c.) stirred at 100°. Stirring was continued at this temperature for a further 3 hours, and the slurry chilled and then drained at the pump; the filtrate was kept for the isolation of the 2 : 6-diaminoxanthone. The precipitate, after extraction with cold dilute sodium hydroxide, consisted of **1 : 7-*diaminoxanthone*** (9·2 g.; m. p. 260°); crystallisation from acetone gave the pure compound in bright yellow needles, m. p. 276° alone and in admixture with a sample prepared by nitration of 1-nitroxanthone and reduction of the product (Found : C, 68·8; H, 4·9; N, 12·5. $C_{13}H_{10}O_2N_2$ requires C, 69·0; H, 4·4; N, 12·4%).

The above acid stannous chloride filtrate was added to 5N-sodium hydroxide, the yellow precipitate collected and redissolved in 5N-hydrochloric acid (50 c.c.), and the filtered solution basified with dilute aqueous ammonia. The precipitate of **2 : 6-*diaminoxanthone*** (1·0 g.; m. p. 282—286°) crystallised from aqueous pyridine in yellow needles, m. p. 318° alone and admixed with material obtained by nitration of 3-nitroxanthone and reduction of the product (Found : C, 68·9; H, 4·7; N, 12·2%).

4 : 3′-*Bisacetamido*-2-*carboxydiphenyl Ether*.—A solution of 2-carboxy-4 : 3′-dinitrodiphenyl ether (10 g.) in aqueous ammonia (100 c.c.; *d* 0·880) was saturated with hydrogen sulphide and then refluxed for 1 hour. The precipitate of sulphur was removed, acetic anhydride (40 c.c.) added during 1 hour to the filtrate stirred at 40°, and the precipitate of **4 : 3′-*bisacetamido*-2-*carboxydiphenyl ether*** (8·6 g.) collected. Recrystallisation from aqueous alcohol gave the pure compound (6 g.) in colourless needles, m. p. 260° (Found : *M*, 327; N, 8·8. $C_{17}H_{16}O_5N_2$ requires *M*, 328; N, 8·6%).

2 : 6-*Diaminoxanthone*.—Cyclodehydration of the foregoing 4 : 3′-bisacetamido-acid (20 g.) followed by deacetylation yielded crude 2 : 6-diaminoxanthone (12 g.; m. p. 296—300°) which separated from dilute pyridine in yellow needles, m. p. 318° (Found : N, 12·6%). This m. p. was not depressed by admixture with a sample prepared as above or by nitration of 3-nitroxanthone followed by reduction; admixture with 1 : 7-diaminoxanthone depressed the m. p. of the latter.

4′-*Acetamido*-2-*carboxy*-4-*nitrodiphenyl Ether*.—A mixture of 2-chloro-5-nitrobenzoic acid (20 g., 0·1 mol.), *p*-hydroxyacetanilide (15 g., 0·1 mol.), anhydrous potassium carbonate (14 g., 0·1 mol.), copper bronze (0·1 g.), cuprous iodide (0·1 g.), and amyl alcohol (150 c.c.) was stirred at the b. p. for 3 hours. The resulting ***diphenyl ether*** (25 g.; m. p. 244°) separated from acetic

acid in golden prisms, m. p. 248° (Found : *M*, 313; N, 8·9. $C_{15}H_{12}O_6N_2$ requires *M*, 316; N, 8·9%).

2 : 7-*Diaminoxanthone*.—A solution of the foregoing crude acetamido-nitro-acid (5 g.) in concentrated sulphuric acid (40 c.c.) was heated at 100° for 2 hours; after cooling, water (10 c.c.) was added and the heating continued for a further 1 hour at 90°. The solution was poured on ice, and the precipitate stirred with a solution of hydrated stannous chloride (30 g.) in 10N-hydrochloric acid (30 c.c.) for 3 hours at 100°. Isolation in the usual way gave **2 : 7-diaminoxanthone** (3 g.) which crystallised from dilute pyridine in long yellow prisms, m. p. 272° alone and in admixture with a sample prepared by direct nitration of xanthone and reduction of the product (Found : N, 12·5%).

***2'-Acetamido-2-carboxy-4-nitrodiphenyl Ether*.**—Condensation of 2-chloro-5-nitrobenzoic acid (20 g.) with *o*-hydroxyacetanilide (16 g.), by the method used for the *p*-isomer, yielded the *diphenyl ether* (6 g.) as pale yellow plates, m. p. 254° (from aqueous alcohol) (Found : *M*, 316; N, 9·1%).

2 : 5-*Diaminoxanthone*.—Cyclisation of the foregoing acid (5 g.) followed by deacetylation and reduction of the product yielded **2 : 5-*diaminoxanthone*** (2·5 g.) which crystallised from alcohol in yellow needles, m. p. 258—260° (Found : C, 69·2; H, 4·6; N, 12·4%).

Series from 2-chloro-3-nitrobenzoic acid.

2 : 5-*Diaminoxanthone*.—A finely ground mixture of 2-chloro-3-nitrobenzoic acid (10 g.), *p*-hydroxyacetanilide (8 g.), anhydrous potassium carbonate (7 g.), copper bronze (0·1 g.), and cuprous iodide (0·1 g.) was heated at 170—175° (oil-bath) for 1 hour. The dark solid mass was extracted with boiling water (100 c.c.), and the filtered solution acidified with hydrochloric acid. The precipitated 4'-acetamido-2-carboxy-6-nitrodiphenyl ether was heated in concentrated sulphuric acid (40 c.c.) at 100° for 1 hour; after cooling and addition of water (10 c.c.) the solution was heated on the water-bath for a further 1 hour and poured on ice (200 g.). The precipitate was heated for 4 hours at 100° with hydrated stannous chloride (30 g.) and 10N-hydrochloric acid (30 c.c.), then poured into 5N-sodium hydroxide. The precipitate of **2 : 5-diaminoxanthone** (4·6 g.) crystallised from alcohol in yellow needles, m. p. 254° alone and admixed with that obtained from the 2'-acetamido-4-nitro-acid (Found : N, 12·5%).

***2-Carboxy-6 : 3'-dinitrodiphenyl Ether*.**—2-Chloro-3-nitrobenzoic acid (20 g., 0·1 mol.), *m*-nitrophenol (14 g., 0·1 mol.), anhydrous potassium carbonate (14 g., 0·1 mol.), and copper bronze (0·5 g.) were stirred with nitrobenzene (120 c.c.) for 4 hours at 160—165° (internal). Treatment in the usual manner gave the crude *diphenyl ether* (20 g.) as pale yellow prisms, m. p. 180—182°, from aqueous alcohol (Found : *M*, 304; N, 9·4. $C_{13}H_8O_7N_2$ requires *M*, 304; N, 9·2%).

1 : 5- *and* 3 : 5-*Dinitroxanthone*.—Cyclodehydration of the foregoing crude acid (20 g.) at 100° with concentrated sulphuric acid (160 c.c.) for 2 hours yielded a mixture of **1 : 5-** and **3 : 5-dinitroxanthones** (16 g.; m. p. 255—275°). This was dissolved in boiling pyridine (150 c.c.); the chilled solution deposited pure **1 : 5-*dinitroxanthone*** (8·4 g.), m. p. 304° not raised by further crystallisation (Found : C, 55·0; H, 2·3; N, 10·0. $C_{13}H_6O_6N_2$ requires C, 54·5; H, 2·1; N, 9·8%).

The pyridine filtrate was heated to the b. p., an equal volume of boiling water added, and the solution cooled. The precipitate, on recrystallisation twice from 50% pyridine, gave **3 : 5-*dinitroxanthone*** (2·8 g.) in plates, m. p. 234° (Found : C, 54·7; H, 2·3; N, 10·1%).

1 : 5- *and* 3 : 5-*Diaminoxanthone*.—Heating the foregoing **1 : 5-dinitroxanthone** (7 g.) with stannous chloride (50 g.) and 10N-hydrochloric acid (50 c.c.) for 3 hours at 100° gave **1 : 5-*diaminoxanthone*** (4·2 g.), yellow needles (from aqueous pyridine), m. p. 266° (Found : C, 69·5; H, 4·5; N, 12·5%).

Reduction of the **3 : 5-dinitroxanthone** (3 g.) in like manner yielded **3 : 5-*diaminoxanthone*** (1·5 g.) which separated from aqueous pyridine in yellow needles, m. p. 268—270°, strongly depressed by admixture of the foregoing **1 : 5-isomeride** (Found : C, 68·8; H, 4·3; N, 12·5%).

***6 : 3'-Bisacetamido-2-carboxydiphenyl Ether*.**—A solution of 2-carboxy-6 : 3'-dinitrodiphenyl ether (18 g.) in water (100 c.c.) and aqueous ammonia (300 c.c.; *d* 0·880) was saturated with hydrogen sulphide and then refluxed for 3 hours. The solution was cooled, the sulphur removed, and the solution adjusted to pH 4·5 with acetic acid. Acetic anhydride (70 c.c.) was added dropwise to the stirred solution which was then cautiously warmed until spontaneous reaction had ceased. After being heated on the water-bath for a further ½ hour the mixture was kept overnight on ice and the precipitate of *bisacetamido-ether* (18 g.; m. p. 240—242°) collected (Found : *M*, 326; N, 8·6. $C_{17}H_{16}O_5N_2$ requires *M*, 328; N, 8·6%).

3 : 5-*Diaminoxanthone*.—Cyclodehydration and deacetylation of the foregoing bisacetamido-acid (15 g.) gave 3 : 5-diaminoxanthone (9·0 g.) which crystallised from 30% aqueous pyridine in fine yellow needles, m. p. 268—270° alone and in admixture with a sample obtained by reduction of 3 : 5-dinitroxanthone (Found : C, 69·3; H, 4·2; N, 12·6%). The m. p. was strongly depressed by admixture with 1 : 5-diaminoxanthone.

6-*Acetamido*-2-*carboxy*-3′-*nitrodiphenyl Ether*.—3-Acetamido-2-chlorobenzoic acid (36 g., 0·16 mol.), *m*-nitrophenol (25 g., 0·18 mol.), potassium carbonate (22 g., 0·16 mol.), copper bronze (0·25 g.), and cuprous iodide (0·25 g.) were stirred with nitrobenzene (200 c.c.) for 5 hours at 155° (internal). The crude product was dissolved in excess of 2·5N-sodium carbonate (100 c.c.), the solution stirred at 50°, and acetic anhydride (25 c.c.) added dropwise during ½ hour. Adjustment to pH 4 with dilute hydrochloric acid effected precipitation of *6-acetamido-2-carboxy-3′-nitrodiphenyl ether* (10 g.; m. p. 224°). A sample crystallised from alcohol in colourless needles, m. p. 227° (Found : *M*, 314; N, 9·0. $C_{15}H_{12}O_6N_2$ requires *M*, 316; N, 8·9%).

5-*Amino*-1-*nitroxanthone* : 1 : 5-*Diaminoxanthone*.—The foregoing acid (8 g.) was heated with sulphuric acid (40 c.c.) at 100° for ½ hour, the solution diluted with water (20 c.c.), and heating continued for a further ½ hour at the same temperature. *5-Amino-1-nitroxanthone* (1·5 g.) was obtained which separated from pyridine in short red needles, m. p. 236° (Found : N, 11·0. $C_{13}H_8O_4N_2$ requires N, 11·0%). Reduction of this (1·0 g.) with stannous chloride (4 g.) and 10N-hydrochloric acid (4 c.c.) for 3 hours yielded 1 : 5-diaminoxanthone which separated from pyridine in yellow needles, m. p. 264—266° alone and in admixture with a sample prepared as above (Found : N, 12·5%).

***Deamination of* 5-*Amino*-1-*nitroxanthone* : 1-*Nitroxanthone*.**—A solution of sodium nitrite (0·28 g.) in concentrated sulphuric acid (2 c.c.) was added dropwise to a solution of 5-amino-1-nitroxanthone (1 g.) in glacial acetic acid (5 c.c.) and sulphuric acid (8 c.c.) stirred at 5°. The solution, after a further 2 hours' stirring, was added dropwise to a stirred suspension of cuprous oxide (1·0 g.; obtained by alkaline reduction of copper sulphate with glucose) in methanol (10 c.c.) at 0°. The mixture was stirred for a further 2 hours at room temperature and poured into water (50 c.c.). Collection of the precipitate, extraction with N-hydrochloric acid (100 c.c.), and crystallisation of the residue three times from toluene gave 1-nitroxanthone (0·2 g.) in pale yellow needles, m. p. 200° alone and in admixture with the compound prepared by cyclisation of 2-carboxy-3-nitrodiphenyl ether (Found : N, 5·9. Calc. for $C_{13}H_7O_4N$: N, 5·8%).

Series from 2-*chloro*-6-*nitro- or* 6-*acetamido*-2-*chloro-benzoic acid.*

2-*Carboxy*-3 : 3′-*dinitrodiphenyl Ether*.—2-Chloro-6-nitrobenzoic acid (10 g., 0·05 mol.), *m*-nitrophenol (10 g., 0·07 mol.), potassium carbonate (7 g., 0·05 mol.), copper bronze (0·1 g.), and cuprous iodide (0·1 g.) were intimately mixed and heated at 170—175° (oil-bath) for 1 hour. The solidified melt was extracted with boiling water (100 c.c.) and the aqueous extract adjusted to pH 3. The precipitated *dinitro-acid* (10 g.) crystallised from aqueous alcohol in colourless plates, m. p. 178—180° (Found : *M*, 304; N, 9·4. $C_{13}H_8O_7N_2$ requires *M*, 304; N, 9·2%). Attempts to cyclise this acid with sulphuric acid, acetic anhydride containing sulphuric acid, phosphoryl chloride, and sulphuric–phosphoric acid failed.

3-*Acetamido*-2-*carboxy*-3′-*nitrodiphenyl Ether*.—A finely ground mixture of 6-acetamido-2-chlorobenzoic acid (11 g., 0·05 mol.), *m*-nitrophenol (8 g., 0·06 mol.), anhydrous potassium carbonate (7·0 g., 0·05 mol.), copper bronze (0·1 g.), and cuprous iodide (0·1 g.) was heated at 170—175° (oil-bath) for 2 hours. Extraction with boiling water (200 c.c.) and acidification of the extract yielded *3-acetamido-2-carboxy-3′-nitrodiphenyl ether* (13 g.) which crystallised from alcohol in golden tablets, m. p. 170—172° (Found : *M*, 315; N, 9·1. $C_{15}H_{12}O_6N_2$ requires *M*, 316; N, 8·8%). This could not be cyclodehydrated with sulphuric acid or acetic anhydride–sulphuric acid.

3 : 3′-*Bisacetamido*-2-*carboxydiphenyl Ether*.—Reduction and acetylation of 2-carboxy-3 : 3′-dinitrodiphenyl ether (10 g.) as for the 6 : 3′-isomer yielded *3 : 3′-bisacetamido-2-carboxydiphenyl ether* (8 g.), m. p. 164° (Found : *M*, 326; N, 8·6. $C_{17}H_{16}O_5N_2$ requires *M*, 328; N, 8·6%).

1 : 6-*Diaminoxanthone*.—Cyclisation of the foregoing acid (4 g.) with sulphuric acid (25 c.c.) followed by deacetylation yielded 1 : 6-diaminoxanthone (1·0 g.) in slender yellow needles, m. p. 254° (Found : N, 12·5%).

Nitroxanthones.

2-*Carboxynitrodiphenyl Ethers*.—These were prepared by stirring the requisite nitro-derivative of *o*-chlorobenzoic acid (80 g.), phenol (100 g.), potassium carbonate (56 g.), nitrobenzene (100 c.c.), copper bronze (0·5 g.), and copper iodide (0·5 g.) at 155° for the time given in

parentheses after the yield. Thus were obtained: 2-Carboxy-4-nitrodiphenyl ether (70 g.; 4 hours), colourless needles, m. p. 172° (from toluene) (Found: *M*, 256; N, 5·6. Calc. for $C_{13}H_9O_5N$: *M*, 259; N, 5·4%) (cf. Purgotti, *Gazzetta*, 1914, **44**, 641). 5-Nitro-acid (72 g.; 7 hours) leaves, m. p. 158° (from aqueous alcohol) (Found: *M*, 258; N, 5·8%) (cf. Ullmann and Wagner, *Annalen*, 1907, **355**, 363). 6-*Nitro-acid* (50 g.; 4 hours), prisms, m. p. 152° (from toluene, (Found: *M*, 259; N, 5·7%).

The following amino-2-carboxydiphenyl ethers were obtained by passing hydrogen sulphide into a solution of the corresponding nitro-acid (20 g.) in aqueous ammonia (*d* 0·880; 100 c.c.) for 2 hours at 20° and then refluxing the solution for 1 hour. After removal of the sulphur the pH of the filtrate was adjusted to pH 4·0 in order to precipitate the amino-acid. The yields were 55—65%.

4-*Amino-*, colourless glistening plates (from water), m. p. 164° (Found: *M*, 225; N, 6·4. $C_{13}H_{11}O_3N$ requires *M*, 229; N, 6·1%). 5-*Amino-*, tablets (from aqueous methanol), m. p. 152° (Found: *M*, 231; N, 6·3%). 6-*Amino-*, golden plates (from aqueous alcohol), m. p. 176° (Found: *M*, 227; N, 6·2%). 3′-*Amino-*, golden plates (from aqueous alcohol), m. p. 150° (Found: *M*, 228; N, 6·2%).

1-*Nitroxanthone*.—2-Carboxy-3-nitrodiphenyl ether (20 g.; Goldberg and Walker, unpublished) was refluxed with phosphoryl chloride (200 c.c.) for 1 hour. Excess of solvent was pumped off, the residual oil poured on ice (250 g.), and the precipitate extracted with dilute sodium carbonate solution. Recrystallisation from aqueous alcohol gave 1-nitroxanthone (10 g.) in colourless plates, m. p. 202° (Found: N, 6·0%). The compound is more accessible by the following route.

o-Chlorobenzoic acid (64 g.), *m*-nitrophenol (56 g.), potassium carbonate (56 g.), and copper bronze were heated together at 160° (bath-temp.) for 4 hours. Isolation *via* the potassium salt yielded *o-m*′-nitrophenoxybenzoic acid (55 g.) which crystallised from 80% alcohol in rhombs, m. p. 138° (Found: *M*, 256; N, 5·5. Calc. for $C_{13}H_9O_5N$: *M*, 259; N, 5·4%) (cf. Dhar, *loc. cit.*). Cyclodehydration of the crude acid (30 g.) with sulphuric acid (150 c.c.) at 100° for 2 hours gave crude 1-nitroxanthone (27 g.) containing *ca.* 10% of the 3-isomeride. Crystallisation from 90% pyridine yielded pure 1-nitroxanthone (22 g.) in pale yellow needles, m. p. 202° alone and in admixture with a sample prepared from 2-carboxy-3-nitrodiphenyl ether (Found: C, 64·4; H, 2·9; N, 6·0%). The pyridine filtrate from the crystallisation was diluted with water and the precipitate crystallised several times from benzene and then aqueous alcohol; 3-nitroxanthone (1·4 g.) was obtained in pale yellow plates, m. p. 170—172° alone and admixed with material obtained by cyclisation of 2-carboxy-5-nitrodiphenyl ether (Found: N, 5·9%).

The following nitroxanthones were prepared by refluxing the crude 2-carboxynitrodiphenyl ether (50 g.) with phosphoryl chloride (400 c.c.) for the time stated after the yield and isolation by the method described for 1-nitroxanthone.

2-Nitroxanthone (41 g.; 8 hours), plates, m. p. 204° (from benzene) (Found: N, 5·9%) (cf. Purgotti and Dhar, *locc. cit.*). 3-Nitroxanthone (40 g.; 7 hours); fawn-coloured needles, m. p. 174° (from aqueous pyridine) (Found: N, 5·8%) (cf. Ullmann and Wagner, *loc. cit.*). 4-Nitroxanthone (38 g.; 4 hours), pale yellow needles, m. p. 190° (from toluene) (Found: N, 6·0, 6·0%) (cf. Dhar, *loc. cit.*, who records m. p. 127°).

4-Nitroxanthone was obtained in the same yield by refluxing 2-carboxy-6-nitrodiphenyl ether (20 g.) in acetic anhydride (100 c.c.) and sulphuric acid (4 c.c.) for 1 hour and pouring the mixture on ice. 2-Carboxy-4-nitrodiphenyl ether by the same method, with a reflux time of 4 hours, gave 2-nitroxanthone in 80% yield. Cyclisation of 2-carboxymononitrodiphenyl ethers, in which the nitro-group is in the carboxylated nucleus, with sulphuric acid at 100° leads to considerable loss of yield by sulphonation. By dissolving 3-carboxy-2-nitrodiphenyl ether (5 g.) in cold sulphuric acid (25 c.c.) and keeping the mixture at room temperature overnight there were obtained 2·4 g. of 2-nitroxanthone.

Aminoxanthones.—The following aminoxanthones were obtained by adding the nitroxanthone (20 g.) during ½ hour to a solution of hydrated stannous chloride (120 g.) in 10N-hydrochloric acid (120 c.c.) stirred at 95—100°. Stirring was continued for 3 hours at this temperature, the mixture kept overnight at 0°, and the magma drained at the pump. The solid was stirred for ½ hour with cold 5N-sodium hydroxide (750 c.c.), and the aminoxanthone collected, washed, and crystallised. The yields in all cases were *ca.* 80%.

1-*Aminoxanthone*, yellow plates (from alcohol), m. p. 148° (Found: C, 73·6; H, 4·3; N, 6·8. Calc. for $C_{13}H_9O_2N$: C, 73·8; H, 4·3; N, 6·6%). 2-Aminoxanthone, yellow needles (from alcohol), m. p. 212° (Found: C, 74·2; H, 4·3; N, 6·8%) (cf. Purgotti, *loc. cit.*; F.P. 821,275). 3-Aminoxanthone, golden prisms (from alcohol), m. p. 230° (Found: N, 6·8%) (cf. Ullmann and

Wagner, *loc. cit.*). 4-Aminoxanthone, pale yellow needles (from toluene), m. p. 202° (Found : C, 73·9; H, 4·3; N, 6·8%) (cf. F.P. 821,275 and 839,698).

Nitration of 4-Nitroxanthone : **2 : 5-***Dinitro- and* **2 : 5-***Diamino-xanthone.*—A solution of nitric acid (9 c.c.; *d* 1·5; 1·1 mol.) in sulphuric acid (30 c.c.; *d* 1·84) was added dropwise to a stirred solution of 4-nitroxanthone (45 g.) in sulphuric acid (200 c.c.) initially at room temperature, that at the end of the addition (30 minutes) being 40°. The solution was heated at 65—70° for a further 1½ hours, then poured on ice, and the precipitate (46 g.; m. p. 200—206°) collected and washed with dilute sodium carbonate and water. Recrystallisation from pyridine gave **2 : 5-***dinitroxanthone* in colourless needles, m. p. 218° (Found : N, 9·9%).

This compound (5 g.) on reduction with hydrated stannous chloride (50 g.) and 10N-hydrochloric acid (50 c.c.) yielded **2 : 5**-diaminoxanthone (3 g.) which separated from aqueous pyridine in elongated yellow needles, m. p. 258—260° alone and mixed with the previous sample (Found : N, 12·6%).

Nitration of 3-Nitroxanthone : **2 : 6-***Dinitro- and* **2 : 6-***Diamino-xanthone.*—To 3-nitroxanthone (24·1 g., 0·1 mol.), dissolved in sulphuric acid (100 c.c.; *d* 1·84) stirred at 10°, nitric acid (4·83 c.c.; *d* 1·5; 0·115 mol.) in sulphuric acid (25 c.c.) was added during ½ hour. The solution was kept at room temperature for a further 2 hours, then heated to 80° during ½ hour, stirred at this temperature for ½ hour, and poured on ice (600 g.). The precipitate was extracted with boiling 2% aqueous sodium carbonate and washed with water (yield, 24 g.; m. p. 230—240°). Crystallisation from aqueous pyridine yielded **2 : 6**-dinitroxanthone, m. p. 268°, alone or mixed with the previous sample (Found : C, 54·6; H, 2·0; N, 10·1%).

Reduction gave **2 : 6**-diaminoxanthone (15 g.), lemon-coloured needles (from dilute pyridine), m. p. and mixed m. p. 320° (Found : C, 68·8; H, 4·6; N, 12·3%).

2-*Carboxy-***5 : 4′-***dinitrodiphenyl Ether* : **2 : 6-***Dinitroxanthone.*—To nitric acid (280 c.c. of *d* 1·42 plus 120 c.c. of *d* 1·50), stirred at 10°, 2-carboxy-5-nitrodiphenyl ether (40 g.) was added during ½ hour, stirring was continued for 5 hours at 15°, and the solution poured on ice (600 g.). The precipitate was washed, boiled with water (1500 c.c.) and calcium carbonate (15 g.) for ½ hour, filtered, evaporated to small volume, and chilled. The crystalline precipitate of the calcium salt was collected (filtrate, 110 c.c.) and stirred on the water-bath for ½ hour with water (250 c.c.) and 10N-hydrochloric acid (50 c.c.) and the **2-***carboxy-***5 : 4′-***dinitrodiphenyl ether* (36 g.; m. p. 148°) collected. This crystallised from toluene in cubes, m. p. 152° (Found : *M*, 304; N, 9·3. $C_{13}H_8O_7N_2$ requires *M*, 304; N, 9·2%). A solution of the crude acid (35 g.) in concentrated sulphuric acid (210 c.c.) was heated on the water-bath for 4 hours, then poured on ice (1 kg.), the precipitate extracted with aqueous sodium carbonate, and the **2 : 6**-dinitroxanthone (25 g.) collected. A sample separated from dilute pyridine in almost colourless needles, m. p. and mixed m. p. 274° (Found : C, 54·0; H, 2·0; N, 9·9%).

The most rapid route to **2 : 6**-dinitroxanthone was the following. 2-Carboxy-5-nitrodiphenyl ether (25·9 g., 0·1 mol.) was dissolved in concentrated sulphuric acid (100 c.c.), stirred at 10—15°; a mixture of nitric acid (4·83 c.c.; *d* 1·5; 0·115 mol.) and sulphuric acid (25 c.c.) was added during ½ hour, the temperature being kept at 10°. Stirring was continued at room temperature for 3 hours, then at 95° for a further 2 hours, the solution poured on ice (400 g.), and the precipitate filtered off. After extraction with dilute potassium carbonate the insoluble crude **2 : 6**-dinitroxanthone (23 g.) was collected. Recrystallisation from dilute pyridine gave the pure compound, m. p. and mixed m. p. 274° (Found : N, 10·0%).

Nitration of 1-Nitroxanthone : **1 : 7-***Dinitroxanthone.*—Nitration of 1-nitroxanthone (9 g.) as described for the 4-isomer yielded crude **1 : 7**-dinitroxanthone (9·8 g.), m. p. 210—220°. This was extracted with a boiling mixture of alcohol (100 c.c.) and pyridine (40 c.c.); the insoluble residue of **1 : 7**-dinitroxanthone (6 g.) on crystallisation from xylene was obtained in yellow plates, m. p. and mixed m. p. 264—266° (Found : C, 54·6; H, 2·0; N, 10·1%).

Reduction of this (10 g.) with stannous chloride (70 g.) and 10N-hydrochloric acid (70 c.c.) gave **1 : 7**-diaminoxanthone (6·5 g.), yellow needles (from acetone), m. p. 276° (Found : N, 12·5%).

Mononitration of Xanthone : **2-***Nitroxanthone.*—Xanthone (19·6 g., 0·1 mol.) was dissolved in sulphuric acid (150 c.c.; *d* 1·84) at 0°. Nitric acid (4·5 c.c.; *d* 1·5; 0·1 mol.) in sulphuric acid (25 c.c.) was added dropwise during ½ hour to the solution stirred at 5°. After a further 2 hours at room temperature the solution was poured on ice (1000 g.), and the precipitate extracted with dilute aqueous sodium carbonate. Extraction with boiling 60% alcohol (150 c.c.) and crystallisation of the insoluble residue from dilute pyridine gave 2-nitroxanthone (15 g.), m. p. and mixed m. p. 204° (Found : N, 5·9%).

Dinitration of Xanthone : **2 : 7-***Dinitroxanthone* (cf. Graebe, and Perkin, *locc. cit.*).—Xanthone

(30 g.) was added portionwise during ½ hour to nitric acid (90 c.c.; *d* 1·5) stirred at 70°. The solution was stirred for a further ½ hour at this temperature, then for 1 hour at 95°, and poured on ice (2 kg.). The colourless solid was washed with boiling water, dried, and extracted for ½ hour with boiling benzene (250 c.c.). The insoluble residue of 2 : 7-dinitroxanthone became crystalline when boiled with methanol (200 c.c.) and pyridine (20 c.c.) (yield, 27 g.; m. p. 262—264°) (Found : C, 54·0; H, 2·0; N, 10·0%).

The benzene extracts from two such nitrations were evaporated and the first fraction (3·5 g.) was removed. The filtrate on evaporation to 150 c.c. and cooling deposited 16 g. of colourless crystals, m. p. 170—182°. Crystallisation from benzene–alcohol–ligroin yielded 2 : 4 : 7-trinitroxanthone (4 g.), m. p. 202—204° (Found : N, 12·7. Calc. for $C_{13}H_5O_8N_3$: N, 12·7%) and a mixture of di- and tri-nitroxanthones (9 g.), m. p. 165—175°.

2 : 7-*Diaminoxanthone*.—Reduction of 2 : 7-dinitroxanthone (50 g.) as described for the 2 : 6-isomeride gave 2 : 7-diaminoxanthone (33 g.; m. p. 272°). Crystallisation from dilute pyridine gave amber-yellow needles, m. p. and mixed m. p. 276° (Found : C, 68·6; H, 4·8; N, 12·6%).

Trinitration of Xanthone : 2 : 4 : 7-*Trinitroxanthone* ("*α-Dinitroxanthone*") (cf. Le Fèvre, *loc. cit.*).—Xanthone (11 g.) was added portionwise during ½ hour to nitric acid (110 c.c.; *d* 1·5), stirred at −5° to 0°, and the solution kept at room temperature for 96 hours and poured into ice-water (500 g.). The colourless precipitate (13·5 g.) was washed, dried, boiled with benzene (400 c.c.), and filtered off at the b. p.; the insoluble residue (6·0 g.) was pure 2 : 7-dinitroxanthone, m. p. 260—262° alone and mixed with that obtained by Graebe's method (*loc. cit.*) (Found : N, 10·0%). The benzene extract on chilling deposited a first crop (3·0 g.), m. p. 202—206° (Found : N, 12·5%); further concentration gave a crop (6·5 g.), m. p. 200° (Found : N, 12·6%). The second crop was shown to be homogeneous by dissolution in benzene and separation into two fractions : 1·8 g., m. p. 198—200° (Found : N, 12·5%), and 4·0 g., m. p. 200—204° (Found : N, 12·5%). Thus, 11 g. of xanthone gave 6·0 g. of 2 : 7-dinitroxanthone and 9·5 g. of 2 : 4 : 7-*trinitroxanthone*. Recrystallisation of the latter from benzene gave leaves, m. p. 202—204°, depressed on admixture with 2 : 4-dinitroxanthone (Ullmann, *Annalen*, **1909**, **366**, 86) obtained by cyclisation of 2-carboxy-4 : 6-dinitrodiphenyl ether (Found : C, 47·3; H, 1·6; N, 12·7. $C_{13}H_5O_8N_3$ requires C, 47·2; H, 1·5; N, 12·7%). The m. p. was not depressed by admixture of the trinitroxanthone obtained by mononitration of 2 : 7-dinitroxanthone or dinitration of 4-nitroxanthone.

Nitration of xanthone (11 g.) as above but for 48 hours gave 2 : 7-dinitroxanthone (6·8 g.), m. p. 264°, a mixture (2·0 g.), m. p. 206—224°, and 2 : 4 : 7-trinitroxanthone (4·5 g.), m. p. 202—204° (Found : N, 12·6%). Nitration for 8 hours then gave 2 : 7-dinitroxanthone (10·5 g.), m. p. 264°, a mixture (1 g.), and 2 : 4 : 7-trinitroxanthone (1·8 g.), m. p. 202° (Found : N, 12·6%).

Mononitration of 2 : 7-*Dinitroxanthone*.—2 : 7-Dinitroxanthone (6 g.) in nitric acid (25 c.c.; *d* 1·5) was heated on the water-bath for 2 hours and poured on ice. The precipitate was dried and boiled with benzene (150 c.c.), and the insoluble residue removed. The filtrate was chilled and the precipitate recrystallised from benzene (150 c.c.); 2 : 4 : 7-trinitroxanthone (3·8 g.) was obtained in colourless leaves, m. p. and mixed m. p. 202—204° (Found : N, 12·6%).

Dinitration of 4-*Nitroxanthone*.—4-Nitroxanthone (6·0 g.) and nitric acid (18 c.c.; *d* 1·5) at 70° (1 hour) and 100° (1 hour) gave a product which was extracted with boiling benzene; the insoluble residue (3 g.) on crystallisation from aqueous pyridine gave 2 : 5-dinitroxanthone (1·6 g.), needles, m. p. 216° (Found : N, 10·0%). The benzene extract on evaporation and chilling yielded material which on recrystallisation from the same solvent gave 2 : 4 : 7-trinitroxanthone (1·0 g.), m. p. 202—204° (Found : N, 12·8%).

2 : 4 : 7-*Triaminoxanthone*.—2 : 4 : 7-Trinitroxanthone (5 g.), stannous chloride dihydrate (60 g.), and 10N-hydrochloric acid (60 c.c.) were heated on the water-bath for 3 hours. The solution was kept at room temperature overnight, then poured into ice (200 g.) and 10N-sodium hydroxide (150 c.c.), and the mixture stirred for 1 hour. The precipitate was washed and crystallised from dilute pyridine, giving 2 : 4 : 7-*triaminoxanthone* (3 g.) as ochre needles, m. p. 252—254° (Found : C, 64·2; H, 4·5; N, 17·4. $C_{13}H_{11}O_2N_3$ requires C, 64·8; H, 4·6; N, 17·4%).

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278. *Tuberculostatic Hydrazides and their Derivatives.*

By Ng. Ph. Buu-Hoï, Ng. D. Xuong, Ng. H. Nam, Fernand Binon, and René Royer.

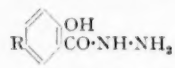
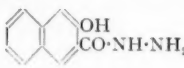
Many new hydrazides and their condensation products with various aldehydes and ketones have been prepared.

Tuberculostatic activity is shown to be widespread in this type of compound, and to be highly dependent on molecular structure.

The antitubercular properties of hydrazines and hydrazides have frequently been investigated (Jouin and Buu-Hoï, *Ann. Inst. Pasteur*, 1946, **72**, 580; Buu-Hoï, Royer, Jouin, Lecocq, and Guettier, *Bull. Soc. chim.*, 1947, **14**, 128; Buu-Hoï, Le Bihan, and Binon, *Rec. Trav. chim.*, 1951, **70**, 1099), and research in this field recently culminated in the discovery of drugs effective in human tuberculosis, notably *iso*nicotinhydrazide (Neoteben, Rimifon, Nydrazid) and its *N'-iso*propyl derivative (Marsalid) (cf. Offe, Siefken, and Domagk, *Naturwiss.*, 1952, **5**, 118; *Deut. med. Woch.*, 1952, **18**, 573; Fox, *Science*, 1952, **116**, 129; Bernstein, Lott, Steinberg, and Yale, *Amer. Rev. Tuberc.*, 1952, **65**, 357). Further, tuberculostatic activity has been shown to be present in a wide series of non-pyridinic hydrazides (Buu-Hoï, Xuong, Nam, and Binon, *Compt. rend.*, 1952, **235**, 329), although no compound has yet been found to approach *iso*nicotinhydrazide in that respect.

The present work records the preparation of a large number of hydrazides and of their condensation products with various aldehydes and ketones. These condensation products were investigated in view of the possibility of their being less toxic than the parent hydrazides, as a result of the blocking of the free NH_2-group.

The aromatic hydrazides found most active hitherto were 5-chlorosalicyl-, 2-hydroxy-1-naphth-, 4-hydroxybenz-, and 1-naphthylacet-hydrazide; 5-chlorosalicylhydrazide possessed a relatively low toxicity and is undergoing *in vivo* tests, especially with strains of *Mycobacterium tuberculosis* resistant to *iso*nicotinhydrazide. All the hydrazides studied gave sparingly soluble chelate compounds with copper salts, and the hypothesis has been put forward that this property might play a rôle in the tuberculostatic effects of hydrazides (Buu-Hoï *et al.*, *Compt. rend.*, 1952, **234**, 1925; 1952, **235**, 329). This theory has now been supported by lack of activity of copper derivatives such as that from 4-hydroxybenzhydrazide and copper sulphate, whereas the free hydrazide is tuberculostatic at a concentration of $1 : 10^{-5}$ (chelation with copper had already been postulated for the tuberculostatic thiosemicarbazones). In view of this hypothesis, compounds containing further chelating groups such as salicylhydrazide (I; R = H), 5-chloro- and 5-bromo-salicyl-

(I)  (II) 

hydrazide (I; R = Cl,Br), and 2-hydroxy-3-naphth-hydrazide (II) and their hydrazones have been specially considered. Table 1 lists the hydrazones prepared from the hydrazides of type (I); Table 2 contains those prepared from 2-hydroxy-3-naphth-hydrazide; Table 3,

Table 1. *Substituted N'-benzylidene (and analogous *) derivatives of* o- *and* p-*hydroxybenzhydrazide.*

Substituents in benzylidene residue	M. p.	Formula	N (%) Found	N (%) Reqd.
Derivatives of salicylhydrazide.				
3 : 4-$(OMe)_2$	197°	$C_{16}H_{16}O_4N_2$	9·2	9·3
2-OH-3-OMe	247	$C_{15}H_{14}O_4N_2$	9·5	9·8
3 : 4-CH_2O_2	271	$C_{15}H_{12}O_4N_2$	9·8	9·9
p-Cl	262	$C_{14}H_{11}O_2N_2Cl$	10·0	10·2
3 : 4-Cl_2 [1]	256	$C_{14}H_{10}O_2N_2Cl_2$	9·2	9·1
o-OH	284	$C_{14}H_{12}O_3N_2$	10·6	10·9
5-Cl-2-OH	287	$C_{14}H_{11}O_3N_2Cl$	9·3	9·6
3 : 5-Cl_2-2-OH [2]	274	$C_{14}H_{10}O_3N_2Cl_2$	8·5	8·6
3 : 5-Br_2-2-OH [3]	261	$C_{14}H_{10}O_3N_2Br_2$	6·6	6·8
3 : 5-I_2-2-OH [4]	258	$C_{14}H_{10}O_3N_2I_2$	5·2	5·5

TABLE 1. (Continued.)

Substituents in benzylidene residue	M. p.	Formula	N (%) Found	N (%) Reqd.
Derivatives of 5-chlorosalicylhydrazide.				
p-OMe	268°	$C_{15}H_{13}O_3N_2Cl$	9·0	9·2
p-OH	286	$C_{14}H_{11}O_3N_2Cl$	9·5	9·6
3 : 4-$(OMe)_2$	239	$C_{16}H_{15}O_4N_2Cl$	8·1	8·4
p-Cl	276	$C_{14}H_{10}O_2N_2Cl_2$	8·8	9·1
3 : 4-CH_2O_2	263	$C_{15}H_{11}O_4N_2Cl$	8·6	8·8
2-OH-3-OMe	266	$C_{15}H_{13}O_4N_2Cl$	8·4	8·7
3 : 4-Cl_2 [5]	264	$C_{14}H_9O_2N_2Cl_3$	8·1	8·2
o-OH	307	$C_{14}H_{11}O_3N_2Cl$	9·4	9·6
5-Cl-2-OH	310	$C_{14}H_{10}O_3N_2Cl_2$	8·3	8·6
3 : 5-Cl_2-2-OH [6]	297	$C_{14}H_9O_3N_2Cl_3$	7·6	7·8
3 : 5-Br_2-2-OH [7]	312	$C_{14}H_9O_3N_2Br_2Cl$	5·9	6·2
3 : 5-I_2-2-OH [8, 19]	319	$C_{14}H_9O_3N_2ClI_2$	5·1	5·2
* 5-Propyl-2-thenylidene [9]	216	$C_{15}H_{15}O_2N_2ClS$	8·5	8·7
Derivatives of 5-bromosalicylhydrazide.				
p-OMe	267	$C_{15}H_{13}O_3N_2Br$	8·1	8·0
p-OH	292	$C_{14}H_{11}O_3N_2Br$	8·1	8·4
3 : 4-$(OMe)_2$	241	$C_{16}H_{15}O_4N_2Br$	7·1	7·4
p-Cl	275	$C_{14}H_{10}O_2N_2BrCl$	7·7	7·9
3 : 4-CH_2O_2	253	$C_{15}H_{11}O_4N_2Br$	7·8	7·7
2-OH-3-OMe	272	$C_{15}H_{13}O_4N_2Br$	7·4	7·7
3 : 4-Cl_2 [10]	274	$C_{14}H_9O_2N_2BrCl_2$	7·0	7·2
o-OH	316	$C_{14}H_{11}O_3N_2Br$	8·2	8·4
5-Cl-2-OH	313	$C_{14}H_{10}O_3N_2BrCl$	7·3	7·6
3 : 5-Cl_2-2-OH [11]	304	$C_{14}H_9O_3N_2BrCl_2$	6·8	6·9
3 : 5-Br_2-2-OH [12]	315	$C_{14}H_9O_3N_2Br_3$	5·5	5·7
* 5-Propyl-2-thenylidene [13]	222	$C_{15}H_{15}O_2N_2BrS$	7·3	7·6
Derivatives of 3 : 5-*dichlorosalicylhydrazide.*[19]				
3 : 5-Cl_2-2-OH [14]	286	$C_{14}H_8O_3N_2Cl_4$	6·8	7·1
3 : 5-Br_2-2-OH [15]	290	$C_{14}H_8O_3N_2Br_2Cl_2$	5·7	5·8
Derivatives of 3 : 5-*dibromosalicylhydrazide.*[19]				
3 : 5-Cl_2-2-OH [16]	238	$C_{14}H_8O_3N_2Br_2Cl_2$	5·5	5·8
3 : 5-Br_2-2-OH [17]	266	$C_{14}H_8O_3N_2Br_4$	4·7	4·9
Derivatives of p-*hydroxybenzhydrazide.*				
o-OH	280	$C_{14}H_{12}O_3N_2$	10·6	10·9
m-OH	271	$C_{14}H_{12}O_3N_2$	10·8	10·9
p-OH	273	$C_{14}H_{12}O_3N_2$	10·5	10·9
p-$CH_2Ph{\cdot}O$	232	$C_{21}H_{18}O_3N_2$	8·2	8·1
3 : 5-I_2-4-OH [18, 19]	270	$C_{14}H_{10}O_3N_2I_2$	5·2	5·5
p-OMe	226	$C_{15}H_{14}O_3N_2$	10·2	10·4
p-NMe_2	251	$C_{16}H_{17}O_2N_3$	14·6	14·8
3 : 4-CH_2O_2	238	$C_{15}H_{12}O_4N_2$	9·7	9·9
Cinnamylidene	232	$C_{16}H_{14}O_2N_2$	10·2	10·5
Citrylidene	140	$C_{17}H_{22}O_2N_2$	9·6	9·8
Glyoxal bis-derivative	300	$C_{16}H_{14}O_4N_4$	17·0	17·1
Derivatives of 3 : 5-*di-iodosalicylhydrazide.*[19]				
o-OH	247	$C_{14}H_{10}O_3N_2I_2$	5·2	5·5
3 : 5-Cl_2-2-OH	244	$C_{14}H_8O_3N_2Cl_2I_2$	4·8	4·9
3 : 5-Br_2-2-OH	268	$C_{14}H_8O_3N_2Br_2I_2$	4·0	4·2
3 : 5-I_2-2-OH	294	$C_{14}H_8O_3N_2I_4$	3·4	3·7

* In derivatives marked thus, the benzylidene group is replaced by that named.

[1] Found: Cl, 22·6. Reqd. Cl, 23·0%. [2] Found: Cl, 21·6. Reqd.: Cl, 21·8%. [3] Found: Br, 38·8. Reqd.: Br, 38·6%. [4] Found: I, 49·6. Reqd.: I, 50·0%. [5] Found: Cl, 31·2. Reqd.: Cl, 31·0. [6] Found: Cl, 29·5. Reqd.: Cl, 29·6%. [7] Found: C, 37·2; H, 2·2. Reqd.: C, 37·5; H, 2·0%. [8] Found: C, 31·2; H, 2·0. Reqd.: C, 31·0; H, 1·7%. [9] Found: S, 9·6. Reqd.: S, 9·9%. [10] Found: C, 43·0; H, 2·4. Reqd.: C, 43·2; H, 2·3%. [11] Found: C, 41·3; H, 2·4. Reqd.: C, 41·6; H, 2·2%. [12] Found: Br, 48·6. Reqd.: Br, 48·7%. [13] Found: S, 8·5. Reqd.: S, 8·7%. [14] Found: Cl, 35·7. Reqd.: Cl, 36·0%. [15] Found: C, 34·5; H, 2·0. Reqd.: C, 34·8; H, 1·7%. [16] Found: C, 34·6; H, 2·0. Reqd.: C, 34·8; H, 1·7%. [17] Found: Br, 56·0. Reqd.: Br, 55·8%. [18] Found: I, 49·6. Reqd.: I, 50·0%. [19] Pale yellow compounds; all the other substances were colourless; recrystallisation from ethanol or propanol. Salicylhydrazide was prepared by Struve and Radenhausen's method (*J. pr. Chem.*, 1895, **52**, 239).

TABLE 2. *Substituted N'-benzylidene (and analogous *) derivatives of 2-hydroxy-3-naphth-hydrazide.*[20]

Substituents in benzylidene residue	M. p.	Formula	N (%) Found	N (%) Reqd.
o-OH	301°	$C_{18}H_{14}O_3N_2$	9·0	9·2
2-OH-3-OMe	272	$C_{19}H_{16}O_4N_2$	8·0	8·3
p-OMe	288	$C_{19}H_{16}O_3N_2$	8·6	8·8
3 : 4-CH_2O_2	236	$C_{19}H_{14}O_4N_2$	8·5	8·4
3 : 5-Cl_2-2-OH [22]	291	$C_{18}H_{12}O_3N_2Cl_2$	7·2	7·5
3 : 5-Br_2-2-OH [23]	295	$C_{18}H_{12}O_3N_2Br_2$	6·1	6·0
3-OMe-4-$OC_{12}H_{25}$-*n*	140	$C_{31}H_{40}O_4N_2$	5·2	5·5
p-NMe_2 [21]	251	$C_{20}H_{19}O_2N_3$	12·8	12·6
p-Cl	266	$C_{18}H_{13}O_2N_2Cl$	8·4	8·6
o-Cl	263	$C_{18}H_{13}O_2N_2Cl$	8·3	8·6
2 : 4-Cl_2 [24]	261	$C_{18}H_{12}O_2N_2Cl_2$	7·6	7·8
3 : 4-Cl_2 [25]	251	$C_{18}H_{12}O_2N_2Cl_2$	7·5	7·8
5-Cl-2-OH	240	$C_{18}H_{13}O_3N_2Cl$	8·0	8·2
* 2-Methoxy-1-naphthylmethylidene [21]	223	$C_{23}H_{18}O_3N_2$	7·3	7·6
* 5-Acenaphthenylmethylidene	258	$C_{24}H_{18}O_2N_2$	7·6	7·7
* 3-Pyrenylmethylidene	262	$C_{28}H_{18}O_2N_2$	6·5	6·8

[20] This hydrazide was prepared by Franzen and Richler's method (*J. pr. Chem.*, 1908, **78**, 164). [21] Yellow prisms; all the other substances were colourless. Recrystallisation from ethanol or propanol. [22] Found: Cl, 18·8. Reqd.: Cl, 18·9%. [23] Found: Br, 34·2. Reqd.: Br, 34·5%. [24] Found: Cl, 19·5. Reqd.: Cl, 19·8%. [25] Found: Cl, 19·6%.

TABLE 3. *Substituted N'-benzylidene (and analogous *) derivatives of thiophen-2-carboxyhydrazides.*

Substituent in benzylidene residue	M. p.	Formula	N (%). Found	N (%). Reqd.
2 : 4-Cl_2 [27]	231°	$C_{12}H_8ON_2Cl_2S$	9·0	9·4
3-OMe-4-$OC_{12}H_{25}$-*n*	112	$C_{25}H_{36}O_2N_2S$	6·0	6·3
3 : 5-I_2-2-OH [26]	dec. 261	$C_{12}H_8O_2N_2I_2S$	5·4	5·6
Derivatives of 5-bromothiophen-2-carboxyhydrazide.				
3 : 4-Cl_2 [28]	237	$C_{12}H_7ON_2BrCl_2S$	7·2	7·4
p-Me	191	$C_{13}H_{11}ON_2BrS$	8·6	8·7
p-NMe_2 [26]	213	$C_{14}H_{14}ON_3BrS$	11·8	11·9
p-OH	245	$C_{12}H_9O_2N_2BrS$	8·4	8·6
o-OH	239	$C_{12}H_9O_2N_2BrS$	8·3	8·6
p-Cl	225	$C_{12}H_8ON_2ClBrS$	8·0	8·1
o-Cl	208	$C_{12}H_8ON_2ClBrS$	8·2	8·1
5-Br-2-OH [29]	232	$C_{12}H_8O_2N_2Br_2S$	6·8	7·0
5-Cl-2-OH	233	$C_{12}H_8O_2N_2BrClS$	7·7	7·8
3 : 5-Cl_2-2-OH	246	$C_{12}H_7O_2N_2Cl_2BrS$	7·0	7·1
3 : 5-I_2-2-OH [26]	255	$C_{12}H_7O_2N_2BrI_2S$	4·6	4·9
2-OH-3-OMe	249	$C_{13}H_{11}O_3N_2BrS$	7·7	7·9
p-OMe	187	$C_{13}H_{11}O_2N_2BrS$	8·1	8·3
5-Propyl-2-thenylidene [26]	154	$C_{13}H_{13}ON_2BrS_2$	7·5	7·8
* 5-Acenaphthenylmethylidene [26]	228	$C_{18}H_{13}ON_2BrS$	7·0	7·3
* 3-Pyrenylmethylidene [26]	288	$C_{22}H_{13}ON_2BrS$	6·2	6·5
Derivatives of 5-chlorothiophen-2-carboxyhydrazide.				
5-Br-2-OH	222	$C_{12}H_8O_2N_2BrClS$	7·6	7·8
2-OH-3-OMe	245	$C_{13}H_{11}O_3N_2ClS$	9·1	9·0
p-NMe_2	207	$C_{14}H_{14}ON_3ClS$	13·6	13·7
o-Cl [30]	210	$C_{12}H_8ON_2Cl_2S$	9·3	9·4
3 : 4-Cl_2 [31]	244	$C_{12}H_7ON_2Cl_2S$	8·1	8·4
o-OH	229	$C_{12}H_9O_2N_2ClS$	9·8	10·0
2 : 4-Cl_2 [32]	227	$C_{12}H_7ON_2Cl_2S$	8·1	8·4
5-Cl-2-OH [33]	219	$C_{12}H_8O_2N_2Cl_2S$	8·7	8·9
3 : 5-I_2-2-OH	264	$C_{12}H_7O_2N_2ClI_2S$	5·1	5·3
3-OMe-4-$OC_{12}H_{25}$-*n*	141	$C_{25}H_{35}O_3N_2ClS$	5·6	5·9
p-OMe	175	$C_{13}H_{11}O_2N_2ClS$	9·2	9·5
m-NO_2	239	$C_{12}H_8O_3N_3ClS$	13·4	13·6
5-*n*-Propyl-2-thenylidene [26]	153	$C_{13}H_{13}ON_2ClS_2$	9·0	9·0
5-Tetradecyl-2-thenylidene	107	$C_{24}H_{35}ON_2ClS_2$	6·2	6·0
5-Acenaphthenylmethylidene [26]	231	$C_{18}H_{13}ON_2ClS$	7·9	8·2
3-Pyrenylmethylidene [26]	288	$C_{22}H_{13}ON_2ClS$	7·0	7·2

* See asterisk to Table 1.

[26] Yellow prisms; all the other substances were colourless. Recrystallisation from ethanol. Thiophen-2-carboxyhydrazide was prepared by Curtius and Thyssen's method (*J. pr. Chem.*, 1902, **65**, 7). [27] Found: Cl, 23·5. Reqd.: Cl, 23·7%. [28] Found: S, 8·2. Reqd.: S, 8·5%. [29] Found: Br, 39·2. Reqd.: Br, 39·6%. [30] Found: Cl, 23·4. Reqd.: Cl, 23·7%. [31] Found: Cl, 31·7. Reqd.: Cl, 13·9%. [32] Found: Cl, 31·8%. [33] Found: Cl, 22·2. Reqd.: Cl, 22·5%.

TABLE 4. *Substituted* N'*-benzylidene (and analogous* *) *derivatives of nicotin- and* iso*nicotin-hydrazide.*

Substituents in benzylidene residue	M. p.	Formula	N (%) Found	N (%) Reqd.
Derivatives of nicotinhydrazide.				
p-OH [34]	248°	$C_{13}H_{11}O_2N_3$	—	—
3 : 4-$(OMe)_2$	158	$C_{15}H_{15}O_3N_3$	14·4	14·7
4-OH-3-OMe [34]	218	$C_{14}H_{13}O_3N_3$	—	—
o-Cl [34]	167	$C_{13}H_{10}ON_3Cl$	—	—
p-Cl	197	$C_{13}H_{10}ON_3Cl$	16·1	16·2
3 : 4-Cl_2 [36]	195	$C_{13}H_9ON_3Cl_2$	14·1	14·3
3-OMe-4-$OC_{12}H_{25}$	126	$C_{26}H_{37}O_3N_3$	9·5	9·6
* 5-Acenaphthenylidene [35]	212	$C_{19}H_{15}ON_3$	13·7	14·0
5-Cl-2-OH	206	$C_{13}H_{10}O_2N_3Cl$	14·9	15·2
o-OH [34]	194	$C_{13}H_{11}O_2N_3$	—	—
3 : 5-Cl_2-2-OH [37]	215	$C_{13}H_9O_2N_3Cl_2$	13·2	13·5
* 3-Pyrenylmethylidene [35]	260	$C_{23}H_{15}ON_3$	12·1	12·0
* Piperonylidene [34]	209	$C_{14}H_{11}O_3N_3$	—	—
* 9-Ethyl-3-carbazolylmethylidene	220	$C_{21}H_{18}ON_4$	16·2	16·4
* 1-Naphthylmethylidene	199	$C_{17}H_{13}ON_3$	15·4	15·3
* 2 : 4-Dichlorophenyl*iso*propylidene [38]	236	$C_{16}H_{13}ON_3Cl_2$	12·2	12·6
Derivatives of iso*nicotinhydrazide.*				
5-Cl-2-OH	232	$C_{13}H_{10}O_2N_3Cl$	15·0	15·2
3 : 5-Cl_2-2-OH [34, 39]	244	$C_{13}H_9O_2N_3Cl_2$	13·2	13·5
3 : 5-Br_2-2-OH [34, 40]	214	$C_{13}H_9O_2N_3Br_2$	10·1	10·5
3 : 5-I_2-2-OH [34, 41]	213	$C_{13}H_9O_2N_3I_2$	8·3	8·5
o-OH [42]	251	$C_{13}H_{11}O_2N_3$	—	—
2-OH-3-OMe	234	$C_{14}H_{13}O_3N_3$	15·2	15·5
p-NMe_2 [34]	199	$C_{15}H_{16}ON_4$	20·8	20·9
3 : 5-I_2-4-OH [34, 43]	dec. >250	$C_{13}H_9O_2N_3I_2$	8·2	8·5
* Cinnamylidene	201	$C_{15}H_{13}ON_3$	16·5	16·7
* 5-Acenaphthenylmethylidene [34]	200	$C_{19}H_{15}ON_3$	14·1	14·0
* 3-Pyrenylmethylidene [34]	259	$C_{23}H_{15}ON_3$	12·2	12·0
* 9-Ethyl-3-carbazolylmethylidene	244	$C_{21}H_{18}ON_4$	16·2	16·4
* 2 : 4-Dichlorophenyl*iso*propylidene [34, 44]	213	$C_{16}H_{13}ON_3Cl_2$	12·4	12·6

* See asterisk in Table 1.

[34] These substances, already reported in the literature (Meyer and Mally, *Monatsh.*, 1912, **33**, 399; Offe, Siefken, and Domagk, *Z. Naturforsch.*, 1952, **7**, [*B*], 462), are listed here in view of the differences in the m. p.s. [35] Yellow compounds; all the others were colourless. [36] Found: Cl, 24·3. Reqd.: Cl, 24·1%. [37] Found: Cl, 22·6. Reqd.: Cl, 22·9%. [38] Found: Cl, 21·0. Reqd.: Cl, 21·3%. [39] Found: Cl, 22·6. Reqd.: Cl, 22·9%. [40] Found: Br, 40·2. Reqd.: Br, 40·1%. [41] Found: I, 51·1. Reqd.: I, 51·5%. [42] Lit., m. p. 247°. [43] Found: I, 51·3. [44] Found: Cl, 21·0. Reqd.: Cl, 21·3%.

those from *N*-2-thenoylhydrazine and its 5-chloro- and 5-bromo-derivative; in Table 4 are listed the hydrazones from nicotin- and *iso*nicotin-hydrazide.

The activity of isatin in the Strecker degradation of amino-acids (cf. Moubasher, *J.*, 1951, 231, 1928) and its selection as a model for carboxylase (see Langenbeck, " Die organischen Katalysatoren," Springer-Verlag, Berlin, 1932) led us to prepare, for biological testing, a number of β-hydrazones derived from isatin (and some of its derivatives) with various hydrazides; these compounds are listed in Table 5.

The tuberculostatic activity *in vitro* of some compounds described in this work has already been reported (Buu-Hoï *et al.*, *locc. cit.*); other results are listed in Table 6.

In view of the high nitrogen content of the hydrazones, determination of nitrogen was more adequate than that of carbon and hydrogen.

EXPERIMENTAL

Halogenated Salicylhydrazides.—A mixture of methyl 5-chlorosalicylate (5 g.), 95% hydrazine hydrate (2·5 g.) and ethanol (50 c.c.) was refluxed for 5 hr.; the precipitate of *5-chlorosalicylhydrazide* formed on cooling (98% yield) crystallised as long, shiny, colourless needles, m. p. 222°, from ethanol (Found: C, 44·9; H, 4·0. $C_7H_7O_2N_2Cl$ requires C, 45·0; H, 3·8%). Similarly were prepared 3 : 5-*dichloro-*, prisms, m. p. 175°, from acetone (Found: C, 37·8; H, 2·9. $C_7H_6O_2N_2Cl_2$ requires C, 38·0; H, 2·7%), *5-bromo-*, needles, m. p. 218°, from ethanol (Found: C, 36·1; H, 3·1. $C_7H_7O_2N_2Br$ requires C, 36·4; H, 3·0%), 3 : 5-*dibromo-*, prisms, m. p. 192°, from acetone (Found: C, 27·0; H, 2·2. $C_7H_6O_2N_2Br_2$ requires C, 27·1; H, 1·9%),

and **3**: *5-di-iodo-salicylhydrazide*, needles, m. p. **218°** (Found: N, 7·0; I, 62·5. $C_7H_6O_2N_2I_2$ requires N, 6·9; I, 62·9%).

β-Naphthyloxyacethydrazide.—This *hydrazide* formed leaflets, m. p. 172°, from ethanol (Found: C, 66·5; H, 5·5. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6%). It gave the following *N'*-derivatives: p-*anisylidene*, prisms, m. p. **182°**, from ethanol–benzene (Found: N, 8·3. $C_{20}H_{18}O_3N_2$ requires N, 8·4%), p-*hydroxybenzylidene*, prisms, m. p. 206°, from ethanol (Found: N, 8·9. $C_{19}H_{16}O_3N_2$ requires N, 8·8%), *piperonylidene*, needles, m. p. 190° (Found: N, 7·8. $C_{20}H_{16}O_4N_2$ requires N, 8·0%), *veratrylidene*, prisms, m. p. 181°, from acetic acid (Found: N, 7·6. $C_{21}H_{20}O_4N_2$ requires N, 7·7%), and p-*chlorobenzylidene*, needles, m. p. 215°, from toluene (Found: N, 8·0. $C_{19}H_{15}O_2N_2Cl$ requires N, 8·3%).

Phenoxyacethydrazide.—This *compound* crystallised as needles, m. p. 108°, from methanol (Found: C, 57·6; H, 6·1. $C_8H_{10}O_2N_2$ requires C, 57·8; H, 6·0%), and gave a p-*anisylidene*, prisms, m. p. 138° (from methanol) (Found: N, 9·5. $C_{16}H_{16}O_3N_2$ requires N, 9·8%); p-*chlorobenzylidene*, m. p. 175° (from toluene) (Found: N, 9·5. $C_{15}H_{13}O_2N_2Cl$ requires N, 9·7%), and *piperonylidene* derivative, prisms, m. p. 201° (from ethanol) (Found: N, 9·5. $C_{16}H_{14}O_4N_2$ requires N, 9·4%).

TABLE 5. *Condensation products of isatins with hydrazides.*[45]

Hydrazide	M. p.	Formula	N (%) Found	N (%) Reqd.	M. p.	Formula	N (%) Found	N (%) Reqd
	Isatin				*5-Methylisatin*			
Phenylacet-	167°	$C_{16}H_{13}O_2N_3$	15·0	15·1				
Dodecan-					130°	$C_{21}H_{31}O_2N_3$	11·5	11·8
β-Naphthyloxyacet-					260	$C_{21}H_{17}O_3N_3$	11·5	11·7
Nicotin-	283	$C_{14}H_{10}O_2N_4$	20·6	21·1	266	$C_{15}H_{12}O_2N_4$	19·6	20·0
*iso*Nicotin-	296	,,	20·8	21·1	316	,,	19·8	20·0
Salicyl-	326	$C_{15}H_{11}O_3N_3$	14·6	14·9	312	$C_{16}H_{13}O_2N_3$	14·0	14·2
5-Chlorosalicyl-	311	$C_{15}H_{10}O_3N_3Cl$	13·0	13·3	316	$C_{16}H_{12}O_3N_3Cl$	12·4	12·7
5-Bromosalicyl	315	$C_{15}H_{10}O_3N_3Br$	11·5	11·7	313	$C_{16}H_{12}O_3N_3Br$	10·9	11·2
2-Hydroxy-3-naphth-	332	$C_{19}H_{13}O_3N_3$	12·4	12·7	323	$C_{20}H_{15}O_3N_3$	12·0	12·2
Adipic bishydrazide	232	$C_{22}H_{20}O_4N_6$	19·1	19·4				
Sebacic bishydrazide	192	$C_{26}H_{28}O_4N_6$	17·3	17·2				
5-Bromothiophen-2-carboxy-	242	$C_{13}H_8O_2N_3BrS$	11·8	12·0				
	5-Bromoisatin				*7-Methylisatin*			
Phenylacet-[46]	228	$C_{16}H_{12}O_2N_3Br$	11·4	11·7				
Dodecan-[47]	166	$C_{20}H_{28}O_2N_3Br$	9·8	10·0				
Phenoxyacet-[48]	201	$C_{16}H_{12}O_3N_3Br$	11·0	11·2				
β-Naphthyloxyacet-	252	$C_{20}H_{14}O_3N_3Br$	9·6	9·9				
Nicotin-[49]	292	$C_{14}H_9O_2N_4Br$	16·0	16·2	195	$C_{15}H_{12}O_2N_4$	19·9	20·0
*iso*Nicotin-[50]	318	,,	15·9	16·2	206	,,	19·8	20·0
Salicyl-[51]	318	$C_{15}H_{10}O_3N_3Br$	11·4	11·7				
					5-Chloroisatin			
5-Chlorosalicyl-	313	$C_{15}H_9O_3N_3ClBr$	10·4	10·6	[52] 314	$C_{15}H_9O_3N_3Cl_2$	11·6	12·0
5-Bromosalicyl-[53]	312	$C_{15}H_9O_3N_3Br_2$	9·3	9·6	309	$C_{15}H_9O_3N_3ClBr$	10·3	10·6
2-Hydroxy-3-naphth-	320	$C_{19}H_{12}O_3N_3Br$	10·0	10·2				
Adipic bishydrazide[54]	233	$C_{22}H_{18}O_4N_6Br_2$	14·4	14·2				
Sebacic bishydrazide[55]	242	$C_{26}H_{26}O_4N_6Br_3$	13·1	130				

[45] The reaction affects the 3-keto-group of isatin (cf. Struve, *J. pr. Chem.*, 1894, **50**, 307). [46] Found: Br, 22·0. Reqd.: Br, 22·3%. [47] Found: Br, 18·8. Reqd.: Br, 19·0%. [48] Found: Br, 21·0. Reqd.: Br, 21·4%. [49] Found: Br, 23·0. Reqd.: Br, 23·2%. [50] Found: Br, 23·1%. [51] Found: Br, 21·9. Reqd.: Br, 22·2%. [52] Found: Cl, 20·2. Reqd.: Cl, 20·3%. [53] Found: Br, 36·2. Reqd.: Br, 36·4%. [54] Found: Br, 26·8. Reqd.: Br, 27·1%. [55] Found: Br, 24·6. Reqd.: Br, 24·8%.

Derivatives of Phenylacethydrazide.—The following derivatives are recorded: p-*anisylidene*, leaflets, m. p. 171°, from methanol (Found: N, 10·2. $C_{16}H_{16}O_2N_2$ requires N, 10·4%); p-*chlorobenzylidene*, needles, m. p. 167°, from methanol (Found: N, 10·2. $C_{15}H_{13}ON_2Cl$ requires N, 10·3%); and *piperonylidene*, needles, m. p. 219°, from ethanol (Found: N, 9·8. $C_{16}H_{14}O_3N_2$ requires N, 9·9%).

Naphthylacethydrazides.—The 1-*naphthyl* compound crystallised as prisms, m. p. 169°, from methanol (Found: N, 13·8. $C_{12}H_{12}ON_2$ requires N, 14·0%); 2-*naphthylacethydrazide* had m. p. 189° (from methanol) (Found: N, 14·2. $C_{12}H_{12}ON_2$ requires N, 14·0%).

3 : 4-*Dichlorocinnamhydrazide*.—3 : 4-Dichlorocinnamic acid was best prepared by a Perkin reaction from 3 : 4-dichlorobenzaldehyde; its *ethyl* ester, prisms, m. p. 81° (from light petroleum) (Found : C, 53·6; H, 4·1. $C_{11}H_{10}O_2Cl_2$ requires C, 53·9; H, 4·1%), gave 3 : 4-*dichlorocinnamhydrazide*, m. p. 138° (from methanol) (Found : N, 12·2. $C_9H_8ON_2Cl_2$ requires N, 12·1%); *ethyl* 2 : 4-*dichlorocinnamate* had m. p. 52° (from light petroleum) (Found : C, 53·8; H, 4·1%).

2-*Hydroxy*-1-*naphth-hydrazide*.—This *compound* formed prisms (from methanol), decomp. >206° (completely melted at 216°) (Found: N, 13·5. $C_{11}H_{10}O_2N_2$ requires N, 13·9%), and gave a 5-*chloro*-2-*hydroxybenzylidene* derivative as prisms, m. p. 240°, from ethanol (Found : N, 8·0. $C_{18}H_{13}O_3N_2Cl$ requires N, 8·2%).

Derivatives of N-*Lauroylhydrazine* (cf. Curtius, *J. pr. Chem.*, 1914, **89**, 511).—The 4-*chlorobenzylidene* derivative formed prisms, m. p. 102°, from ethanol (Found : N, 8·0. $C_{19}H_{29}ON_2Cl$ requires N, 8·3%); and the p-*dimethylaminobenzylidene* derivative pale yellow needles, m. p. 103°, from methanol (Found : N, 12·0. $C_{21}H_{35}ON_3$ requires N, 12·2%).

TABLE 6. *Tuberculostatic activities* in vitro.[a]

	Activity at concn. 1 in
N'-4-Hydroxybenzylidene*iso*nicotinhydrazide[b]	10^{-7}
N'-5-Chloro-2-hydroxybenzylidene*iso*nicotinhydrazide	10^{-7}
N'-5-Bromo-2-hydroxybenzylidene*iso*nicotinhydrazide	10^{-6}
N'-Cinnamylidene*iso*nicotinhydrazide	10^{-7}
N'-*p*-Chlorophenyl*iso*propylidene*iso*nicotinhydrazide	10^{-7}
N'-2 : 4-Dichlorophenyl*iso*propylidene*iso*nicotinhydrazide	10^{-6}—10^{-7}
N'-3 : 4-Methylenedioxybenzylidenephenylacethydrazide	$<10^{-4}$
N'-4-Hydroxy-3-methoxybenzylidenephenylacethydrazide	$<10^{-4}$
N'-3 : 4-Dimethoxybenzylidenephenylacethydrazide	$<10^{-4}$
p-Hydroxy-*N'*-*o*-hydroxybenzylidenebenzhydrazide	10^{-4}
p-Hydroxy-*N'*-*m*-hydroxybenzylidenebenzhydrazide	10^{-4}
p-Hydroxy-*N'*-*p*-hydroxybenzylidenebenzhydrazide	10^{-4}—10^{-5}
N'-Anisylidene-*p*-hydroxybenzhydrazide	10^{-5}
4-Hydroxy-*N'*-*p*-methoxyphenyl*iso*propropylidenebenzhydrazide	10^{-4}
N'-Citrylidene-*p*-hydroxybenzhydrazide	10^{-4}
N'-*p*-Dimethylaminobenzylidene-*p*-hydroxybenzhydrazide	$<10^{-4}$
N'-3-Chloro-4-hydroxybenzylidene-*p*-hydroxybenzhydrazide	10^{-4}
p-Hydroxy-*N'*-(4-hydroxy-3 : 5-di-iodobenzylidene)benzhydrazide	10^{-4}
N'-*p*-Chlorophenyl*iso*propylidene-*p*-hydroxybenzhydrazide	10^{-4}
N'-Cinnamylidene-*p*-hydroxybenzhydrazide	10^{-4}
Glyoxal bis-(*p*-hydroxybenzoylhydrazone)	$<10^{-4}$
Glucose *p*-hydroxybenzoylhydrazone	$<10^{-4}$
5-Chloro-*N'*-*p*-methoxybenzylidenesalicylhydrazide	10^{-4}
5-Chloro-*N'*-*p*-chlorobenzylidenesalicoylhydrazide	10^{-4}
N'-*p*-Anisylidene-5-bromosalicoylhydrazide	10^{-4}
5-Bromo-*N'*-*p*-chlorobenzylidenesalicylhydrazide	10^{-4}
N'-*p*-Anisylidene-β-naphthyloxyacethydrazide	10^{-4}
Complex from *p*-hydroxybenzhydrazide and $CuSO_4$	$<10^{-4}$
p-Hydroxybenzhydrazide	10^{-5}
2 : 5-Dihydroxy*iso*nicotinhydrazide	$<10^{-4}$
Pyrazinecarboxyhydrazide	10^{-5}

[a] Determined on *Mycobacterium tuberculosis var. hominis*, strain H37 Rv, in Dubos–Middlebrook medium (the inoculum was a 6-day old culture on Dubos medium, and the reading was taken after 3 weeks). [b] The high activity found for this substance is in accord with a recent work of Offe, Siefken and Domagk (*Z. Naturforsch.*, 1952, **7**, [*B*], 465).

Nicotin- and iso*Nicotin-hydrazide*.—These hydrazides were prepared by 30 min.' refluxing of a solution of the corresponding methyl ester (60 g.) and 95% hydrazine (15 g.) in ethanol (50 c.c.); after cooling, the precipitated hydrazide was collected and recrystallised from ethanol. Methyl nicotinate and *iso*nicotinate were conveniently prepared as follows : a mixture of the acid (80 g.), methanol (300 c.c.), benzene (300 c.c.), and sulphuric acid (60 c.c.) was refluxed for 2 hr.; next, the azeotropic mixture of methanol, benzene, and water was slowly distilled off (4—5 hr.); the viscous residue (100 c.c.) was poured on ice (150 g.) and basified with sodium carbonate to pH 8, and the free ester taken up in chloroform (yield, 72 g.).

Derivatives of Adipic and Sebacic Dihydrazides.—Adipic dihydrazide was prepared by Curtius' method (*J. pr. Chem.*, 1915, **91**, 4). It gave the following derivatives : *di*-p-*chlorobenzylidene*, leaflets, m. p. 248°, from ethanol (Found : N, 13·1. $C_{20}H_{20}O_2N_4Cl_2$ requires N, 13·4%); *di*-p-*methoxybenzylidene*, leaflets (from ethanol), m. p. 217° (Found : N, 13·4. $C_{22}H_{26}O_4N_4$ requires N, 13·7%); *dipiperonylidene*, needles, m. p. 234° (from ethanol) (Found : N, 12·6. $C_{22}H_{22}O_6N_4$ requires N, 12·8%); *divanillylidene*, prisms, m. p. 287° (from ethanol)

(Found : N, 12·8. $C_{22}H_{26}O_6N_4$ requires N, 12·7%); *bis*-(p-*dimethylaminobenzylidene*), needles, m. p. 224° (from ethanol) (Found : N, 19·1. $C_{24}H_{32}O_2N_6$ requires N, 19·3%); and *di*-5-*acenaphthenylmethylidene*, pale yellow leaflets, m. p. 212° (from ethanol) (Found : N, 11·0. $C_{32}H_{30}O_2N_4$ requires N, 11·2%). Sebacic dihydrazide (Steller, *J. pr. Chem.*, 1900, **62**, 216) gave the following derivatives: *di*-p-*chlorobenzylidene*, leaflets, m. p. 209° (from ethanol) (Found : N, 11·9. $C_{24}H_{28}O_2N_4Cl_2$ requires N, 11·8%); *di*-p-*methoxybenzylidene*, leaflets, m. p. 182° (from ethanol) (Found : N, 12·2. $C_{26}H_{34}O_4N_4$ requires N, 12·0%); *dipiperonylidene*, leaflets, m. p. 203° (from ethanol) (Found : N, 11·0. $C_{26}H_{30}O_6N_4$ requires N, 11·3%); *bis*-(p-*dimethylaminobenzylidene*, prisms, m. p. 164° (from ethanol) (Found : N, 16·9. $C_{25}H_{40}O_2N_6$ requires N, 17·1); and *di*-5-*acenaphthenylmethylidene*, faintly yellow leaflets, m. p. 194° (from ethanol) (Found : N, 10·2. $C_{36}H_{38}O_2N_4$ requires N, 10·0%).

n-*Dodecyl Vanillyl Ether*.—Prepared by alkylation of vanillin with *n*-dodecyl bromide and potassium hydroxide in ethanol, this *ether* had b. p. 256—258°/18 mm., and formed prisms, m. p. 57°, from ethanol (Found : C, 74·8 ; H, 10·1. $C_{20}H_{32}O_3$ requires C, 75·0; H, 10·0%); its *thiosemicarbazone* formed needles, m. p. 128°, from ethanol (Found : C, 64·0; H, 9·0. $C_{21}H_{35}O_2N_3S$ requires C, 64·1; H, 8·9%), its *semicarbazone* needles, m. p. 142°, from ethanol (Found : N, 11·0. $C_{21}H_{35}O_3N_3$ requires N, 11·1%), and its 4-*keto*-2-*thiazolinylhydrazone*, m. p. 188°, from acetic acid (Found : C, 63·4; H, 8·3. $C_{23}H_{35}O_3N_3S$ requires C, 63·7; H, 8·1%).

Other Hydrazines.—Further *compounds*, prepared by analogous methods, are recorded in the Tables.

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279. *Epimeric Alcohols of the* cyclo*Hexane Series. Part IX.** (±)-cis-3-*Methyl*cyclo*hexylmethanol and* (±)-cis-3-*Methyl*cyclo*hexanecarboxylic Acid.*

By L. H. DARLING, A. KILLEN MACBETH, and J. A. MILLS.

Mixtures of varying proportions of the epimers of 3-methyl*cyclo*hexanecarboxylic acid have been prepared by the hydrogenation of *m*-toluic acid under different conditions, and by the catalytic hydrogenation of (±)-3-methyl-*cyclo*hex-1-enecarboxylic acid. Purification through the piperazine salt gives pure (±)-*cis*-3-methyl*cyclo*hexanecarboxylic acid. Hydrogenolysis in the presence of copper chromite of the ethyl ester gives (±)-*cis*-3-methyl*cyclo*hexylmethanol, which was purified through the 3 : 5-dinitrobenzoate. Only one of the epimeric pairs of the acid, and of the alcohol, has been isolated, and the configuration rests on the unambiguous synthesis of the *cis*-alcohol which has recently been carried out by Haggis and Owen (*J.*, 1953, 408).

Systematic crystallisation of the 1-menthylphthalamic ester led to the resolution of the (±)-carbinol, upwards of 20 per cent. of (+)-*cis*-3-methyl-*cyclo*hexylmethanol being obtained.

THE 2-methyl*cyclo*hexanecarboxylic acids and the related carbinols have already been described by Macbeth, Mills, and Simmonds (*J.*, 1949, 1011), and the 4-methyl compounds by Cooke and Macbeth (*J.*, 1939, 1245). Both acids were prepared by catalytic hydrogenation of the corresponding toluic acids, the carbinols being derived by the hydrogenolysis of the esters of the alicyclic acids. The epimeric acids and alcohols were isolated, and the *cis*- and *trans*-configurations were assigned on the basis of the Auwers–Skita rule (Auwers, *Annalen*, 1919, **420**, 89; 1920, **421**, 1; Skita, *ibid.*, 1922, **427**, 255; *Ber.*, 1920, **53**, 1792; 1922, **55**, 144). Haggis and Owen (*loc. cit.*) have confirmed the configurations by their recent synthesis of the alcohols by a series of stereochemically specific steps.

* Part VIII, *J.*, 1949, 1717.

The study has now been extended to the 3-methyl*cyclo*hexanecarboxylic acids and the corresponding *cyclo*hexylmethanols. Several preparations of 3-methyl*cyclo*hexanecarboxylic acid have been recorded but in most cases the product was a mixture of the epimers and no effort was made to isolate either pure. A liquid acid was obtained by the sodium–*iso*amyl alcohol reduction of *m*-toluic acid (Markownikoff and Hagemann, *J. pr. Chem.*, 1894, **49**, 71; Perkin and Tattersall, *J.*, 1905, **87**, 1090). Similar products were obtained from 3-chloro- or 3-iodo-methyl*cyclo*hexane (Zelinsky, *Ber.*, 1902, **35**, 2689; Gutt, *ibid.*, 1907, **40**, 2061). Mousseron and Granger (*Bull. Soc. chim.*, 1946, 246) reported that the action of hydrochloric acid on (±)-*trans*-3-methyl*cyclo*hexanol gave (±)-*cis*-1-chloro-3-methyl*cyclo*hexane whereas the use of phosphorus pentachloride gave the *trans*-compound. When the magnesium derivatives of the halides were carbonated the so-called *cis*- and *trans*-3-methyl*cyclo*hexanecarboxylic acids were obtained. These were characterised by anilides. Later (*Bull. Soc. chim.*, 1947, 605), these workers prepared the (−)-*cis*- and the (+)-*trans*-acid from the active 1-chloro-3-methyl*cyclo*hexanes, the acids being purified by fractional distillation of their methyl esters.

We do not regard preparation through the halogen compounds as an altogether reliable method as we found that the methyl*cyclo*hexanecarboxylic acid, obtained from 3-methyl*cyclo*hexanol through the chloride (prepared by the action of hydrochloric acid), contains considerable quantities of 4-methyl*cyclo*hexanecarboxylic acid, identical with the *trans*-acid, prepared by Cooke and Macbeth (*loc. cit.*); migration evidently takes place during the formation of the chloro-compound. Palfray and Rothstein (*Compt. rend.*, 1929, **189**, 701; **190**, 942) also experienced migration when *cyclo*hexane-1 : 3-diol was heated with hydrochloric acid, as 1 : 4-dichloro*cyclo*hexane and 4-chloro*cyclo*hexanol were isolated. Other preparations of the 3-methyl acid have been described by Wallach (*Annalen*, 1912, **389**, 194) and by Mousseron and Granger (*Compt. rend.*, 1944, **218**, 358). In only a few cases have crystalline derivatives of the acid been prepared. These derivatives therefore appear to be of no great value in the characterisation of the acid.

Samples of the mixed epimers of (±)-3-methyl*cyclo*hexanecarboxylic acid were obtained, with d_4^{30} varying from 0·9951 to 0·9971, by the catalytic hydrogenation of *m*-toluic acid under different conditions. In other experiments, hydrogenation of (±)-3-methyl*cyclo*hex-1-enecarboxylic acid in the presence of Raney nickel gave a mixture (d_4^{30} 0·9988) of the epimeric acids, and hydrogenation with platinum oxide in glacial acetic acid gave a mixture (d_4^{30} 0·9977).

Repeated crystallisation of the piperazine salt was found to be the most satisfactory method for the purification of the mixed acids, but some 10 recrystallisations from anhydrous acetone were necessary before a salt of constant m. p. was obtained. The purified piperazine salt on hydrolysis gave (±)-*cis*-3-methyl*cyclo*hexanecarboxylic acid, which was further characterised by the preparation of an amide, an anilide, and a *p*-bromophenacyl ester. Only the one epimer could be isolated from the various mixtures, and all attempts to obtain the acid of higher density, from the mother-liquors obtained during the purification of the piperazine salt, were unsuccessful. The amide and some metallic salts were also fractionally crystallised without success.

Little attention has been directed to the 3-methyl*cyclo*hexylmethanols and no solid ester appears to have been prepared. Skita (*loc. cit.*) prepared a mixture of the inactive alcohols in 28% yield by the sodium–ethanol reduction of the ethyl 3-methyl*cyclo*hexanecarboxylate, and Mousseron and Granger reduced the methyl esters of the so-called (−)-*cis*- and (+)-*trans*-acids mentioned above to get the corresponding carbinols. The purity of these alcohols is in doubt as no attempt was made at purification through crystalline derivatives. In the present work the mixed acids obtained by the hydrogenation methods were esterfied with ethanol and sulphuric acid and the resulting ester was, after purification, hydrogenolysed in the presence of a copper chromite catalyst. Attempts to purify the resulting alcohol through its hydrogen phthalate were unsuccessful, but crystallisation of the crude 3 : 5-dinitrobenzoate gave an ester, m. p. 81·5—82° which on hydrolysis gave pure (±)-*cis*-3-methyl*cyclo*hexylmethanol, which was characterised by the preparation of a number of esters. We did not succeed in separating the epimeric alcohol from any of our mixtures.

The application of the Auwers–Skita rule appears to find favour generally in the case of 1 : 2- and 1 : 4-disubstituted *cyclo*hexanes: and other workers also associate higher energy content and higher entropy with the *cis*-compound. Haggis and Owen (*loc. cit.*) have synthesised *cis*- and *trans*-2- and *trans*-4-methyl*cyclo*hexylmethanols by a series of stereochemically specific steps, and the identity of their products with those previously prepared has shown the validity of the application of the Auwers–Skita rule in assigning these configurations (Cooke and Macbeth; Macbeth, Mills, and Simmonds, *locc. cit.*).

On the other hand several significant cases have been recorded in which the Auwers–Skita rule is undoubtedly reversed for 1 : 3-disubstituted *cyclo*hexanes. von Auwers and Schmelzer (*Chem. Zentr.*, 1927, II, 1562) queried the validity of the rule for 3-methyl*cyclo*hexylamines; Skita and Rossler (*Ber.*, 1939, **72**, 265) found that the resolvable hexahydro*iso*phthalic acid (*trans*; the *cis*-acid has a plane of symmetry) had in fact the higher density and refractive index. Skita and Faust (*Ber.*, 1939, **72**, 1127) showed that *trans*-3 : 5-dimethyl*cyclo*hexanol, which was also capable of resolution, had a higher refractive index than the inactive isomer: and Mousseron and Granger (*Compt. rend.*, 1938, **207**, 367; *Bull. Soc. chim.*, 1938, 1618; 1946, 218) provided similar arguments in the case of the 1 : 3-dimethyl*cyclo*hexanes.

A more critical approach to the question of isomerism must therefore be made in the case of the 1 : 3-disubstituted *cyclo*hexanes. Consideration of the substitution of the equatorial and polar hydrogen atoms in the more stable, chair form of *cyclo*hexanes (Pitzer *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 977, 2488; Hassel and Ottar, *Acta Chem. Scand.*, 1947, **1**, 929; Hassel and Furberg, *ibid.*, 1950, **4**, 597) indicates that of the pairs of geometrical isomers the one possessing lower density, lower refractive index, etc., has the lesser steric hindrance: and the lower physical constants are associated with *trans*-1 : 2- and -1 : 4- but *cis*-1 : 3-disubstituted *cyclo*hexanes. Rossini and Pitzer (*Science*, 1947, **105**, 647) accordingly proposed the relabelling of the 1 : 3-dimethyl*cyclo*hexanes, and it is likely that a similar step should be taken for the 3-methyl*cyclo*hexanols (Macbeth and Mills, *J.*, 1945, 709; 1947, 205). On this basis the *cis*-configuration should be assigned to the (±)-3-methyl*cyclo*hexanecarboxylic acid now described, as it has a much lower density than that of any of the mixtures of the epimers obtained in the hydrogenations: and the related alcohol should also be regarded as being the *cis*-form. The matter has been placed beyond doubt by Haggis and Owen's (*loc. cit.*) unambiguous synthesis of *cis*-3-methyl*cyclo*hexylmethanol and its identity with the alcohol now described.

The resolution of the *cis*-alcohol was attempted so that comparison could be made with the optically active alcohols described by Mousseron and Granger (*loc. cit.*). Crystallisations of the alkaloidal salts of the hydrogen phthalate of the racemic alcohol did not provide a method, but resolution was successfully carried out by recrystallisation of the (−)-menthylphthalamate. In this way more than 20% of (+)-*cis*-3-methyl*cyclo*hexylmethanol was isolated, but we failed to obtain the (−)-*cis*-alcohol.

Experimental

Hydrogenation of m-*Toluic Acid over Raney Nickel.*—The sample was purified by treating an alkaline solution of *m*-toluic acid with charcoal and crystallising the acid liberated on acidification. The acid [from ethanol–water (1 : 4)] had m. p. 111—112°. The Raney nickel used was prepared according to Pavlic and Adkins (*J. Amer. Chem. Soc.*, 1946, **68**, 1471). (a) *Alkaline hydrogenation.* In a typical experiment *m*-toluic acid (40 g.) in sodium hydroxide (9%; 140 ml.) containing Raney nickel (4 g.) was shaken with hydrogen at 1840 lbs./sq. in. at an initial temperature of 18°. The temperature was raised to 165° during 50 minutes, and this temperature was maintained until the hydrogenation was completed (2 hours in all). After removal of the catalyst, the solution was poured into an excess of 10% hydrochloric acid, and the separated oil was extracted with ether. After drying ($MgSO_4$) and removal of the solvent the 3-methyl*cyclo*hexanecarboxylic acid was distilled; it had b. p. 139—143°/20 mm., d_4^{30} 0·9971 (yield 38·5 g., 92%). When less pure *m*-toluic acid or less active catalyst was used the time of hydrogenation was increased and the yields were not so good, but the density of the product was substantially the same.

(b) *Neutral solution.* Pure *m*-toluic acid (40 g.) with an equivalent of sodium hydroxide

(9%; 131 ml.) and Raney nickel (4 g.) was hydrogenated (3 hours) at 190°. The product (38 g.) had b. p. 91—94°/0·75 mm., d_4^{30} 0·9992.

Hydrogenation of m-*Toluic Acid over Platinum Oxide.*—The catalyst was prepared according to Adams, Voorhees, and Shriner (*Org. Synth.*, Coll. Vol. I, 1941, 463). Pure *m*-toluic acid (10 g.), in redistilled acetic acid (100 ml.), and catalyst (0·5 g.), were shaken with hydrogen at room temperature and atmospheric pressure. After nearly 6 hours almost the theoretical amount (5 l.) of hydrogen had been absorbed. After filtration and washing of the catalyst with light petroleum (60—90°), the solvent was removed from the combined filtrates, and the crude acid distilled. The product (9·6 g., 92%) had b. p. 98—99°/1·2 mm., d_4^{30} 0·9950.

Hydrogenation of 3-*Methyl*cyclo*hex*-1-*enecarboxylic Acid.*—The acid was prepared *via* the nitrile from 3-methyl*cyclo*hexanone cyanohydrin, and was characterised as the *piperazine* salt, flat, white crystals (from acetone), m. p. 157·5—159° (decomp.) (Found: N, 7·55. $C_{20}H_{34}O_4N_2$ requires N, 7·6%), and as the p-*bromophenacyl* ester, m. p. 86—87° (from aqueous methyl alcohol) (Found: Br, 23·3, 23·5. $C_{16}H_{17}O_3Br$ requires Br, 23·7%).

(a) *Raney nickel catalyst.* The acid (13 g.) in sodium hydroxide solution (9%; 42 ml.) and water (30 ml.) was hydrogenated in the presence of Raney nickel (3 g.) as described above for *m*-toluic acid; 3-methyl*cyclo*hexanecarboxylic acid (12 g., 92%), d_4^{20} 0·9988, was obtained.

(b) *Platinum oxide catalyst.* The unsaturated acid (6·2 g.) in glacial acetic acid (70 ml.) was hydrogenated in the presence of platinum oxide catalyst (0·3 g.) as described above for *m*-toluic acid. The product (5·2 g.) had b. p. 91—92°/0·5 mm., d_4^{20} 0·9977.

Piperazine Salt of (±)-cis-3-*Methyl*cyclo*hexanecarboxylic Acid.*—The mixture of the epimeric acids (20 g.) from the hydrogenation in alkaline solution in the presence of Raney nickel was dissolved in dry acetone (15 ml.), and anhydrous piperazine (6·1 g.) in dry acetone (25 ml.) was added, the mixture being heated on the water-bath under reflux for 5 minutes. After cooling, the salt was filtered off, washed with dry acetone (10 ml.), and dried at about 70°. The salt (25·2 g., 92%), m. p. 92—98°, was repeatedly recrystallised from dry acetone and ultimately gave the pure *piperazine* salt of (±)-*cis*-3-methyl*cyclo*hexanecarboxylic acid (7·9 g., 30%), m. p. 113—114° (Found: C, 65·0; H, 10·35; N, 7·65. $C_{20}H_{38}O_4N_2$ requires C, 64·85; H, 10·05; N, 7·6%).

Similar preparations were carried out with the mixed acids obtained in the other hydrogenations, and in all cases the salt was identical with that described above.

(±)-cis-3-*Methyl*cyclo*hexanecarboxylic Acid.*—The piperazine salt (7·8 g.) was decomposed by shaking it with hydrochloric acid (3%; 180 ml.) and ether (50 ml.). (±)-*cis*-3-Methyl*cyclo*hexanecarboxylic acid (5·4 g., 90%) had b. p. 93°/0·8 mm., d_4^{30} 0·9921, $n_D^{20°}$ 1·4570; it was characterised by the following derivatives: p-*bromophenacyl* ester, plates (from aqueous methanol), m. p. 93—94° (Found: Br, 23·3. $C_{16}H_{19}O_3Br$ requires Br, 23·55%); *amide*, pearly plates (from benzene), m. p. 160° (Found: N, 9·95. $C_8H_{15}ON$ requires N, 9·95%); and *anilide*, clusters of fine needles [from petroleum (b. p. 100—120°)], m. p. 128—129° (Found: N, 6·4. $C_{14}H_{19}ON$ requires N, 6·45%).

Halogenation of 3-*Methyl*cyclo*hexanol and Preparation of the Carboxylic Acid.—Migration to* trans-4-*methyl*cyclo*hexanecarboxylic acid.* A sample (46 g.) of 3-methyl*cyclo*hexanol rich in the *trans*-epimer was heated with fuming hydrochloric acid (Borsche and Lange, *Ber.*, 1907, **40**, 2222) (300 ml.) with stirring under reflux on a boiling-water bath. After 5 hours the solution was cooled, and the chloride extracted with ether and distilled under reduced pressure. Part of the chloride (27 g.) was converted into a Grignard reagent which was carbonated (Gilman and Kirby, *Org. Synth.*, Coll. Vol. I, 1932, 353) to the carboxylic acid (23 g., 70%), b. p. 143—145°/14·8 mm., d_4^{30} 0·9926, n_D^{20} 1·4572. The piperazine salt was prepared as described above and after 10 crystallisations reached a constant m. p., 162—163°, which was not depressed when the salt was mixed with the piperazine salt prepared from *trans*-4-methyl*cyclo*hexanecarboxylic acid [Cooke and Macbeth (*loc. cit.*)] (Found: N, 7·65, 7·3. Calc. for $C_{20}H_{38}O_4N_2$: N, 7·6%). The piperazine salt gave *trans*-4-methyl*cyclo*hexanecarboxylic acid, m. p. 110—111° not depressed on admixture with an authentic sample.

(±)-cis-3-*Methyl*cyclo*hexylmethanol.*—(a) *Preparation of ethyl* (±)-cis-3-*methyl*cyclo*hexanecarboxylate.* The ethyl ester (43 g., 95%) was prepared by refluxing the acid (37·5 g.) with ethanol (380 ml.) and sulphuric acid (3·5 ml.) for 1 hour. The mixture was slowly fractionated [more ethanol being added dropwise during the fractionation], then concentrated (to 100 ml.) and extracted with ether.

(b) *Hydrogenolysis of the ester.* Copper chromite catalyst (6·5 g.) was suspended in the ester (63 g.) and the mixture shaken with hydrogen at 1720 lbs./sq. inch, the temperature being gradually increased to 250° during 2 hours, then maintained at 250° for 3·5 hours. The alcohol

was recovered in the usual way and distilled under reduced pressure. The hydrogen phthalate was unsatisfactory for purification, but the 3 : 5-dinitrobenzoate proved suitable. This was prepared from the alcohol (49 g.), in pyridine (34 ml.) and dry benzene (80 ml.), and 3 : 5-dinitrobenzoyl chloride (106 g.) in dry benzene (340 ml.). The crude dinitrobenzoate (118 g., m. p. 54—68°) was systematically crystallised from ethanol, giving pale yellow well-defined orthorhombic crystals of (±)-cis-3-*methyl*cyclo*hexylmethyl* 3 : 5-*dinitrobenzoate* (51 g.), m. p. 81·5—82° (Found : N, 8·6. $C_{15}H_{18}O_6N_2$ requires N, 8·7%).

(c) *Hydrolysis of* (±)-cis-3-*methyl*cyclo*hexylmethyl* 3 : 5-*dinitrobenzoate*. The pure 3 : 5-dinitrobenzoate (30 g.) was dissolved in methanol (150 ml.) and refluxed for 30 minutes with potassium hydroxide (7 g.), dissolved in the minimum amount of water. Water (100 ml.) was then added and most of the methanol was removed by distillation. The residue was distilled with steam, and the alcohol obtained by extraction with light petroleum (b. p. 40—50°). (±)-*cis*-3-Methyl*cyclo*hexylmethanol (10·5 g., 88%) had b. p. 47—48°/0·4 mm., d_4^{30} 0·8896, n_D^{20} 1·4585. It was characterised by the following derivatives : *phenylurethane*, lustrous plates (from aqueous methanol), m. p. 73·5—74·5° (Found : N, 5·75. $C_{15}H_{21}O_2N$ requires N, 5·65%); *α-naphthylurethane*, needles (from aqueous methanol), m. p. 81—81·5° (Found : N, 4·9. $C_{19}H_{23}O_2N$ requires N, 4·7%); *hydrogen phthalate*, prismatic crystals (from carbon tetrachloride), m. p. 120—121° (Found : C, 69·4; H, 7·05. $C_{16}H_{20}O_4$ requires C, 69·55; H, 7·3%); p-*nitrobenzoate*, m. p. 35—36° (Found : N, 7·05. $C_{15}H_{19}O_4N$ requires N, 5·05%); and allophanate, fine needles (from acetone), m. p. 177—178°.

Ethyl 3-methyl*cyclo*hex-1-enecarboxylate was subjected to simultaneous hydrogenation and hydrogenolysis in the presence of copper chromite catalyst. Only the *cis*-alcohol was obtained on purification through the 3 : 5-dinitrobenzoate.

Resolution of (±)-cis-3-*Methyl*cyclo*hexylmethanol*.—(a) The inactive alcohol (8 g.) was heated with stirring at 50—60° with phthalic anhydride (10·2 g.) and pyridine (A.R.; 15 ml.) for 4·5 hours. The cooled mixture was poured into hydrochloric acid (10%; 40 ml.) and water (100 ml.), and the solution extracted with benzene. The hydrogen phthalate was transferred from the washed benzene solution into sodium carbonate solution (5%; 200 ml.), and this was acidified with hydrochloric acid (10%; 27 ml.) and the liberated ester taken up in chloroform. The solvent was removed from the washed and dried extract, and the residue was crystallised from carbon tetrachloride, giving the hydrogen phthalate (16·5 g.), m. p. 120—121°. Brucine, strychnine, and quinine salts of the ester were prepared, but repeated crystallisation failed to achieve any resolution.

(b) Thionyl chloride (2·1 ml.) in ether (15 ml.) was added with stirring to (−)-menthylphthalamic acid (8·7 g.) in anhydrous ether (70 ml.) and pyridine (2·3 ml.) during 30 minutes, and stirring continued for a further hour. The inactive alcohol (3·7 g.) was then added, followed during 30 minutes by pyridine (2·3 ml.) in anhydrous ether (25 ml.). The mixture was stirred for another hour and kept overnight. Removal of the solvent from the washed, dried ethereal solution gave the crude ester (9·9 g., 84%, m. p. 80—100°). Yields up to 97% were obtained in larger scale experiments. Fifteen crystallisations of the crude ester from light petroleum (b. p. 60—90°) gave pure (+)-*cis*-3-methyl*cyclo*hexylmenthyl (−)-methylphthalamate, m. p. 140—141° (yield 23%, based on the inactive alcohol).

The ester (8·8 g.) in methanol (25 ml.) was heated under reflux for 30 minutes after the addition of potassium hydroxide (1·6 g., in water 2 ml.). Most of the methanol was removed under reduced pressure and the residue distilled with steam. The distillate was extracted with light petroleum (b. p. 50—60°) and, after removal of the solvent, the alcohol was distilled under reduced pressure. (+)-*cis*-3-Methyl*cyclo*hexylmethanol (2·3 g., 85%), had b. p. 84°/7·5 mm., d_4^{30} 0·8997, n_D^{20} 1·4585, $[\alpha]_D^{14}$ +4·94° (homogeneous).

It was characterised by the following derivatives: *phenylurethane*, fine needles (from aqueous methanol), m. p. 78—79° (Found: C, 72·9, 73·05; H, 8·4, 8·6; N, 5·8%); *α-naphthylurethane*, needles (from aqueous methanol), m. p. 101·5—102° (Found : C, 76·5; H, 7·9; N, 4·85%); 3 : 5-*dinitrobenzoate*, white, pearly plates (from ethanol), m. p. 75—76° (Found : C, 55·95; H, 5·55; N, 8·95%); and *hydrogen phthalate*, m. p. 127—128° (Found : C, 69·2; H, 7·3%).

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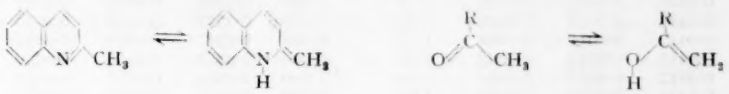
280. *ω-Halogenomethyl-pyridines, -quinolines, and -isoquinolines. Part IV.* The Mechanism of Halogenation of Quinaldines.*

By B. R. Brown, D. Ll. Hammick, B. H. Thewlis, and D. J. Walbridge.

It is found that ωω-dibromoquinaldine in acetic acid containing sodium acetate is brominated at 30° to ωωω-tribromoquinaldine at a rate which is independent of the concentration of bromine and of acetate. The analogy between this phenomenon and the acid-catalysed halogenation of ketones is discussed and conclusions as to the mechanism are drawn.

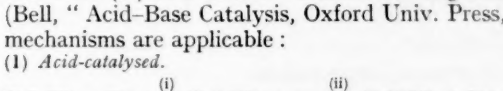
Many reactions of α- and γ-methyl-pyridines and -quinolines are similar to the prototropic reactions of methyl ketones, *e.g.*, Claisen condensation in presence of a base (Wislicenus and Kleisinger, *Ber.*, 1909, **42**, 140; Bergstrom and Moffatt, *J. Amer. Chem. Soc.*, 1937, **59**, 1494), aldol condensation with an aldehyde in the presence of an acid (Jacobsen and Reimer, *Ber.*, 1883, **16**, 2606), and ready bromination of the methyl group in acetic acid in presence of sodium acetate (Koenigs, *Ber.*, 1898, **31**, 2364; Hammick, *J.*, 1923, **123**, 2882; Brown, Hammick, and Thewlis, Part I, *J.*, 1951, 1145). Mills and Smith (*J.*, 1922, 2724) have suggested that the methylene base (I) is an intermediate in these reactions, analogous to the



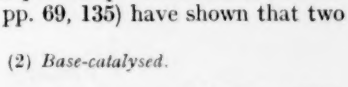
(I) (II)

enol form (II) of a ketone. Kinetic investigations of the prototropic reactions of ketones (Bell, " Acid–Base Catalysis, Oxford Univ. Press, 1941, pp. 69, 135) have shown that two mechanisms are applicable :

(1) *Acid-catalysed.*



(2) *Base-catalysed.*



It appeared not improbable that α- and γ-methyl-pyridines and -quinolines might react by similar mechanisms, and the special example of bromination has been investigated kinetically under the preparative conditions, *viz.*, in acetic acid in presence of sodium acetate (Part I, *loc. cit.*).

Experimental

The rate of disappearance of bromine in acetic acid containing bromine, ωω-dibromoquinaldine, and sodium acetate was followed colorimetrically at λ 5200 Å by means of a Hilger–Nutting spectrophotometer. Preliminary experiments showed that the colour density–concentration variation is linear for bromine in acetic acid. The simple Beer's law relation could not, however, be used to ascertain bromine concentrations in the reaction mixtures because, when Br^- ions are produced, residual free bromine is progressively converted into Br_3^- ions; the extinction coefficient of Br_3^- at 5200 Å is less than that of the bromine molecule (Rurakayastha, *J. Indian Chem. Soc.*, 1929, 361). A series of calibration curves was therefore constructed. Thus the optical density of an initial solution containing bromine $[Br_2]_0$ and sodium acetate $[OAc^-]_0$ was determined. A series of solutions was then made up containing progressively less bromine but with enough sodium bromide added to maintain the quantity $[Br_2] + [Br^-]$ equal to the initial bromine concentration $[Br_2]_0$. Sodium acetate was then added to make the total ionic strength in each solution equal to the original, *i.e.*, $[OAc^-]_0$. The conditions existing in a reaction run were thus duplicated. The optical densities were measured and plotted against bromine concentration giving a smooth curve. If there be present in the original bromine solution $[Br_2]_0$ an appropriate concentration of ωω-dibromoquinaldine, the rate of bromination of the latter can be followed by determinations of optical

* Part III, *J.*, 1952, 1186.

density and reference to the calibration curve, which will give the total concentration of free plus ionic bromine at time t. From the stoicheiometry of the reaction the amount of dibromoquinaldine that has been brominated is obtained.

Kinetic Measurements.—The reaction rates were measured at 30·0°. The initial concentration of each reactant was varied, the other two being constant and in excess. The variations in concentration were: bromine, 0·0175—0·0639M; dibromoquinaldine, 0·0050—0·0300M; anhydrous sodium acetate, 0·0050—0·100M. All reagents and the solvent were purified by normal procedures; control experiments were carried out which showed no appreciable interaction of bromine with solvent either alone or containing sodium acetate. The error in optical density measurement corresponded to an error in estimation of bromine of ±0·0002M. As explained above, the amount of ωω-dibromoquinaldine $(a - x)$ present at time t could be obtained from the optical density and the appropriate calibration curve; these values were substituted in the equation $k_{mono} = (1/t) \cdot \ln a/(a - x)$. The unimolecular constant was sensibly the same in all cases. In Table 1 we give the results obtained in a typical run. In Table 2 the results of all our experiments are summarised.

TABLE 1. *Initial concs. : dibromoquinaldine,* 0·0100M; *sodium acetate,* 0·0200M.

t (sec.)	Br (mole/l.)	x	$(a - x)$	10^4k (sec.$^{-1}$)	t (sec.)	Br (mole/l.)	x	$(a - x)$	10^4k (sec.$^{-1}$)
0	0·0433	—	—	—	3,900	0·0384	0·0049	0·0051	1·75
300	0·0428	0·0005	0·0095	1·70	4,500	0·0380	0·0053	0·0047	1·70
600	0·0423	0·0010	0·0090	1·70	5,100	0·0373	0·0060	0·0040	1·80
900	0·0419	0·0014	0·0086	1·70	6,000	0·0367	0·0066	0·0034	1·80
1200	0·0415	0·0018	0·0082	1·65	6,900	0·0363	0·0070	0·0030	1·75
1500	0·0413	0·0020	0·0080	1·50	7,800	0·0356	0·0077	0·0023	1·90
2100	0·0405	0·0028	0·0072	1·60	8,700	0·0352	0·0081	0·0019	1·90
2700	0·0400	0·0033	0·0067	1·50	10,500	0·0349	0·0084	0·0016	1·75
3300	0·0391	0·0042	0·0058	1·65					

$k = 1·70 \times 10^{-4}$ sec.$^{-1}$

TABLE 2.

Variation of initial bromine concentration.

Initial concns. : sodium acetate, 0·070M; dibromoquinaldine, 0·070M.

Initial Br concn. (mole/l.)	0·0175	0·0331	0·0433	0·0545	0·0639
10^4k (sec.$^{-1}$)	1·90	1·70	1·80	1·80	1·80

Variation of initial dibromoquinaldine concentration.

Initial concns. : sodium acetate, 0·020M; bromine, 0·0433M.

Initial dibromoquinaldine concn. (mole/l.)	0·0050	0·0100	0·0200	0·0300
10^4k (sec.$^{-1}$)	1·60	1·70	1·55	1·70

Variation of initial sodium acetate concentration.

Initial concns. : bromine, 0·0433M; dibromoquinaldine, 0·020M.

$[NaOAc]_0$ (mole/l.)	0·0050	0·0100	0·0200	0·0400	0·0600	0·100
10^4k (sec.$^{-1}$)	1·80	1·80	1·55	1·70	1·80	1·70

ωω-*Dibromo*-8-*nitroquinaldine* (Hammick, *J.*, 1926, 1302).—The compound separated from ethanol as pale yellow needles, m. p. 184°.

ωω-*Dibromo*-5-*nitroquinaldine.*—5-Nitroquinaldine (Gerdiessen, *Ber.*, 1889, **22**, 245) (6·0 g.) and anhydrous sodium acetate (20 g.) were dissolved in glacial acetic acid (30 ml.), and bromine (3·25 g.) in acetic acid (25 ml.) was added with stirring, the temperature not being allowed to rise above 70°. Towards the end of the reaction yellow ωω-*dibromo*-5-*nitroquinaldine* separated. The mixture was cooled and the dibromonitro-compound (5·0 g.) separated. Three recrystallisations from ethanol yielded pale yellow needles, m. p. 161° (Found: C, 34·7; H, 1·6; N, 7·8; Br, 46·9. $C_{10}H_6O_2N_2Br_2$ requires C, 34·7; H, 1·7; N, 8·0; Br, 46·2%).

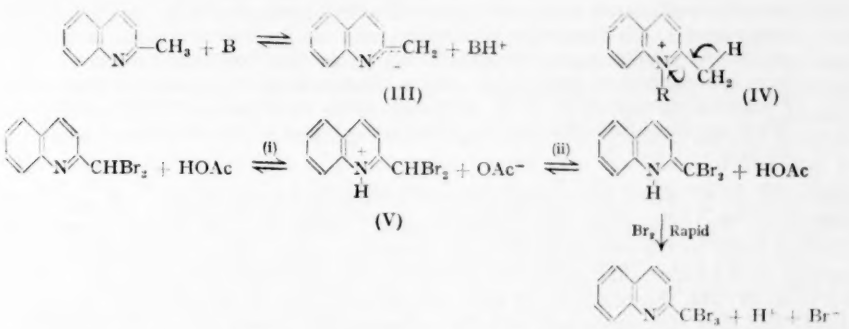
The rate constants for the bromination of these two dibromonitroquinaldines were determined at 30·0° as for dibromoquinaldine itself. Mean values were: ωω-dibromo-8-nitroquinaldine, $8·0 \times 10^{-4}$ sec.$^{-1}$; ωω-dibromo-5-nitroquinaldine, $0·40 \times 10^{-4}$ sec.$^{-1}$

DISCUSSION

The rate of bromination of ωω-dibromoquinaldine in acetic acid in presence of sodium acetate is independent of the bromine concentration (Table 2). This is exactly analogous to the acid- or base-catalysed bromination of ketones and indicates that the rate-

determining step is probably a catalysed prototropic change followed by rapid bromination of the intermediate. Also the rate is independent of the concentration of acetate ion (Table 2). The reaction does not therefore involve a rate-determining base-catalysed prototropic change of the dibromoquinaldine molecule as was previously thought (Part I, *loc. cit.*).

In the light of other reactions of the α- and γ-methylquinolines this result appears less surprising, since the majority of the base-catalysed reactions, *e.g.*, the Claisen condensation (Wislicenus and Klesinger, Bergstrom and Reimer, *locc. cit.*), require much stronger bases than the acetate ion to produce the intermediate mesomeric ion (III). Also, the aldol condensation with aldehydes does not occur with basic catalysts (Mills and Roper, *J.*, 1925, 2466). On the other hand, in the quaternary salts (IV) the nitrogen atom carries a fixed positive charge which should facilitate the release of a proton from the α-carbon atom. Thus quinaldine condenses with benzaldehyde in the presence of acids (Jacobsen and Reimer, *loc. cit.*), and quinaldine ethiodide condenses with benzaldehyde in the presence of piperidine whereas quinaldine itself does not (Mills and Roper, *loc. cit.*). Furthermore, ω-bromination of lepidine has not proved possible, but its methiodide is smoothly brominated in aqueous sodium acetate (Part I, *loc. cit.*).



Since ωω-dibromoquinaldine must exist mainly as the quaternary salt (V) in excess of glacial acetic acid, its bromination is interpreted as an acid-catalysed prototropic change followed by rapid bromination of the intermediate methylene base, a process entirely analogous to the acid-catalysed bromination of ketones. The function of the sodium acetate is thus to remove hydrogen bromide, which, in the absence of acetate, causes a reduction in the rate of bromination by the removal of the reactant dibromoquinaldine as its insoluble hydrobromide. In the analogous reaction with ketones [(1), p. 1369] Zucker and Hammett (*J. Amer. Chem. Soc.*, 1939, **61**, 2785) have obtained evidence that step (ii) is rate-determining, since the rate constants are independent of the basic strengths of a series of ketones. Thus, as Zucker and Hammett (*loc. cit.*) point out, the rate-determining step of this acid-catalysed mechanism is one in which a base removes a proton from a point remote from the basic centre. A similar effect may occur with the quinaldines, since, as was inferred in Part I (*loc. cit.*), the progressive ω-substitution of halogen atoms, which decreases the basic strength, increases the rate of substitution. This is readily explained if the rate-determining step is the removal of a proton by a base from the α-carbon atom.

The rates of reaction of ωω-dibromoquinaldine and of its 5- and 8-nitro-derivatives with bromine in acetic acid in presence of sodium acetate are in the predicted order of proton release from the α-carbon atom, but since the basic strengths of these compounds are unknown, it cannot be said that this represents unequivocal evidence for the rate-determining step of the bromination.

It has not been possible to investigate the catalytic effect of strong acids in acetic acid since their addition results in precipitation of the reactant as an insoluble acid salt. Acetic acid was chosen as solvent since it is itself not attacked by bromine under the experimental conditions; it was moreover desirable to investigate the reaction under the preparative

conditions. It is not possible to investigate the reaction in water because in that solvent the salts of dibromoquinaldine are partly hydrolysed with precipitation of the base. However, the investigation of a suitable soluble quaternary salt in water should reveal a reaction which shows general basic catalysis.

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281. *Polyene Acids. Part VI.* A New* (cis-trans-)*Isomer of Sorbic Acid and its Relation to Hexenolactones.*

By ULLI EISNER, J. A. ELVIDGE, and R. P. LINSTEAD.

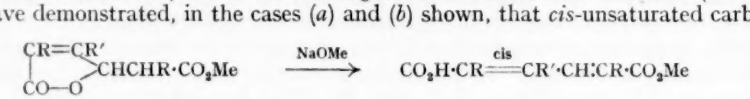
Ring fission of the δ-hexenolactone (II) (racemic parasorbic acid) with methanolic sodium methoxide yields *cis-trans*-sorbic acid, m. p. 35°: its liquid methyl ester is a by-product. The acid has been characterised as the *S*-benzylthiuronium salt, converted into the amide, benzylamide, morpholide, and *iso*butylamide, and reduced to hexanoic acid.

The diene structure of the new acid is shown by the oxidation of its amide to oxalic and oxamic acids, the quantitative hydrogenation of the amide to hexanoamide, the ultra-violet absorption, and the inversion to sorbic acid effected by irradiation or hot alkali. The geometrical configuration follows from the method of preparation and is confirmed by a preparation from 5-hydroxyhex-*cis*-2-enoic acid, obtained from hexenolactone (II) with dilute aqueous alkali and also by semihydrogenation of 5-hydroxyhex-2-ynoic acid.

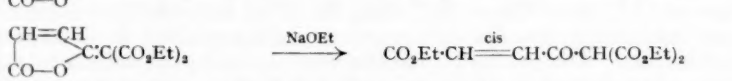
SORBIC ACID, m. p. 134·5°, was among the first unsaturated acids known. It was obtained in 1859 by A. W. Hofmann of this College (*Annalen*, 1859, **110**, 129) by the action of alkali or mineral acids on the rowan-berry oil or parasorbic acid. With dilute alkalis, the oily parasorbic acid yielded amorphous salts from which it was regenerated by acid. Doebner (*Ber.*, 1894, **27**, 344) showed that the salts were derived from an unsaturated hydroxy-acid, $C_6H_{10}O_3$, and that parasorbic acid was the corresponding lactone (I) or (II), isomeric with sorbic acid. Sorbic acid was identified as hexa-2 : 4-dienoic acid (Fittig and Barringer, *Annalen*, 1872, **161**, 307; Kachel and Fittig, *ibid.*, 1873, **168**, 276; Doebner, *Ber.*, 1890, **23**, 2372), and much later the lactone was shown to be (+)-hex-2-eno-δ-lactone (Kuhn and Jerchel, *Ber.*, 1943, **76**, 413). The steric configuration of sorbic acid is all-*trans* (see below).

We have demonstrated, in the cases (*a*) and (*b*) shown, that *cis*-unsaturated carboxylic

(*a*) [1,2,3]

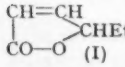


(*b*) [4]



[1] R = R′ = H; *J.*, 1950, 2235. [2] R = H, R′ = Me; *J.*, 1951, 3386.
[3] R = Me, R′ = H; *J.*, 1952, 1026. [4] *J.*, 1951, 1501.

products are formed by the ring-fission of αβ-unsaturated γ-lactones with sodium alkoxides at room temperature. We therefore examined the ring-opening of hex-2-eno-δ-lactone (II) and the isomeric γ-lactone (I) (Δ$^{\alpha}$-homoangelicalactone), in order to determine whether a new (*cis*-)isomer of sorbic acid might be obtained under conditions milder than those applied by Hofmann to parasorbic acid.



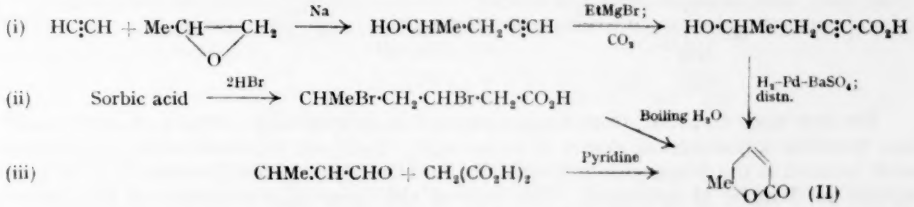
(I)

Synthetic racemic hex-2-eno-δ-lactone was used. Of the methods (i)—(iii) [(i) Haynes and Jones, *J.*, 1946, 503, 954; (ii) Kuhn and Jerchel, *loc. cit.*; (iii) Joly and Amiard, *Bull. Soc. chim.*, 1947, 139] for its preparation, the first was most satisfactory. Method (ii) was simpler but the first stage inconveniently slow. Method (iii) gave mainly sorbic acid, with some lactone which was difficult to isolate. The structure of the product, m. p.

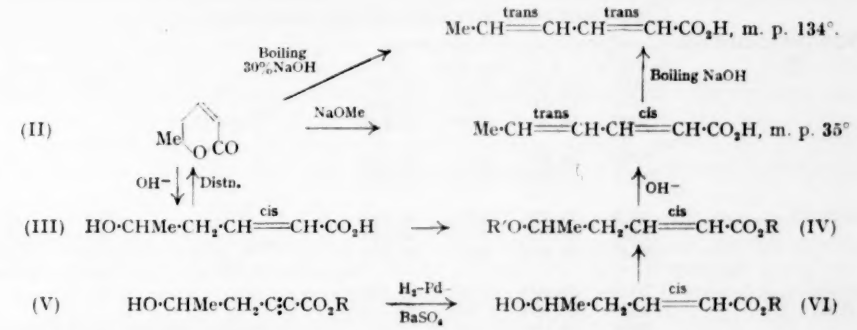
* Part V, *J.*, 1953, 708.

13°, given by route (ii) was proved by Kuhn and Jerchel. Haynes and Jones recorded a boiling point and refractive index similar to those given by Kuhn and Jerchel but no melting point. We have crystallised the lactonic products from the routes (i) and (ii) and confirmed their identity.

The synthetic racemic lactone (II), like the natural (+)-compound, afforded (ordinary) sorbic acid in good yield when treated with boiling 30% sodium hydroxide. Dissolution of the lactone in warm barium or potassium hydroxide, followed by double decomposition with *S*-benzylthiuronium chloride, gave the crystalline thiuronium salt of an unsaturated


(i) HC:CH + Me·CH—CH2 (O) Na HO·CHMe·CH2·C:CH EtMgBr; CO2 HO·CHMe·CH2·C:C·CO2H
(ii) Sorbic acid 2HBr CHMeBr·CH2·CHBr·CH2·CO2H H2–Pd–BaSO4; distn.
Boiling H2O
(iii) CHMe:CH·CHO + CH2(CO2H)2 Pyridine Me O CO (II)

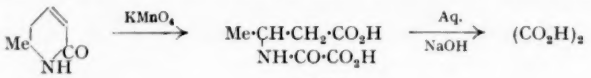
hydroxy-acid (cf. Doebner, *Ber.*, **1894**, **27**, 344), which we have shown to be racemic 5-hydroxyhex-*cis*-2-enoic acid (III). The acid itself was isolated comparatively pure as an oil. It could be titrated with cold 0·05N-alkali, which was without effect upon hexenolactone, it formed a crystalline cinchonidine salt, and with diazomethane gave the methyl ester, characterised as the 3 : 5-dinitrobenzoate [IV; R = Me, R′ = $CO·C_6H_3(NO_2)_2$]. The hydroxy-acid did not lactonise spontaneously, or in boiling ether, but did so on distillation. By semihydrogenation of the acetylenic ester (V; R = Et), Haynes and Jones (*J.*, 1946, 954) prepared ethyl 5-hydroxyhex-2-enoate (VI; R = Et) which was therefore presumably the racemic *cis*-compound. In boiling hydrochloric acid it afforded racemic hexenolactone (II). We have now prepared the methyl acetylenic ester (V; R = Me) and thence by semi-hydrogenation methyl 5-hydroxyhex-*cis*-2-enoate (VI; R = Me). This gave a 3 : 5-dinitrobenzoate identical with that from the hydroxy-acid (III) produced from hexenolactone and barium hydroxide. The *cis*-structure (III) is therefore certain.



With sodium methoxide in methanol, hexenolactone gave (as expected) an isomeric carboxylic acid, $C_6H_8O_2$, m. p. 35°. A by-product was the corresponding methyl ester, also prepared from the new acid and diazomethane. The new acid was easily soluble in organic liquids, and formed a highly crystalline *S*-benzylthiuronium salt, m. p. 137°. This, however, was unstable on repeated crystallisation, whilst the acid itself quickly resinified : it could however be kept at 0°, under nitrogen. The amide and benzylamide of the acid were stable : the morpholide was an oil and the *iso*butylamide a low-melting solid, both of which soon polymerised. The corresponding amides of sorbic acid were distinct substances, all solids : the sorbic morpholide and *iso*butylamide resinified rapidly.

The unsubstituted amide of the new acid had a melting point (113°) close to that (108°)

of a product with the same formula, prepared at 200° from ammonia and sorbic acid or hexenolactone (Fischer and Schlotterbeck, *Ber.*, 1904, **37**, 2357; Kuhn and Jerchel, *loc. cit.*). However, a mixed melting point, and the ultra-violet light absorption characteristics, indicated that the compounds were not identical. The high-temperature reaction product was shown by Kuhn and Jerchel to be a dihydro-6-methyl-2-pyridone, and they suggested that the double bond was in the 3 : 4-position, as in (VII). This we have proved by oxidising the compound to an acid, $C_6H_9O_5N$, which on hydrolysis gave oxalic acid in good yield. The intermediate acid was evidently β-oxaloamidobutyric acid (VIII).



(VII) (VIII)

The new acid, m. p. 35°, from hexenolactone was undoubtedly a hexa-2 : 4-dienoic acid and therefore a geometrical isomer of sorbic acid. Catalytic reduction afforded hexanoic acid, isolated as the *S*-benzylthiuronium salt; and the amide yielded hexanoamide with an uptake of 2 mols. of hydrogen. This proved the open-chain structure of the amide. Oxidation of the new amide with permanganate gave oxalic and oxamic acids, which proved that the two double bonds were in the αβ- and the γδ-position. Moreover, the new acid and its amides showed ultra-violet light absorption typical of a conjugated diene-acid : the positions of the maxima were close to those for the corresponding (all *trans*-)sorbic derivatives, but the intensities were lower (see Table). The infra-red spectra of the two *iso*butylamides (which have no insecticidal activity) showed the following distinctive bands (cm.$^{-1}$) in Nujol :

cis-trans	1268 (infl.)	1253	1226	1155	997	961	928	834
trans-trans	1261	1156	990	942	867			

The new isomeric acid was rapidly inverted in boiling 30% aqueous sodium hydroxide to sorbic acid but was not inverted by boiling water. In cold alkali, inversion occurred very slowly. Hydrolysis of the amide with boiling alkali was accompanied by inversion and sorbic acid was obtained.

Ultra-violet absorption characteristics in ethanol.

CHMe:CH·CH:CH·COR	*cis*(αβ)-*trans*(γδ)		*trans-trans*	
R	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε
OH	2510	16,200	2510 [1]	27,400
	2570	17,000	2570	27,400
	2600	16,200	2630	25,800
NH_2	2510	22,200	2510	27,200
	2570	22,200	2570	27,200
$NH·CH_2Ph$	2500	27,500	2500	32,200
	2570	29,100	2570	34,600
	2630	27,500	2620	32,200
$N<^{[CH_2]_2}_{[CH_2]_2}>O$	2510	15,900	2570	26,800
	2570	18,100	2650	28,100
	2640	18,100	—	—
	2790	10,300	—	—
$NHBu^t$	2510	23,400	2510 [2]	29,600
	2570	25,400	2570	31,300
	2640	20,000	2630	29,600
OMe	2510	15,700	2580 [3]	31,500
	2570	17,400	—	—
	2640	15,700	—	—

$\lambda_{max.}$ (Å) ε
2050 [4] 10,700

2360	2,600
2470	2,600
2510	2,600
2560	2,200

[1] Hauser, Smakula, and Kuhn (*Z. physikal. Chem.*, 1935, **29**, *B*, 371) record $\lambda_{max.}$ 2610 Å, ε = 25,000. [2] Crombie, *Chem. and Ind.*, 1952, 1034. [3] D. G. O'Sullivan, Thesis, London, 1947, p. 77. [4] Haynes and Jones (*J.*, 1946, 954) give ε 10,000 at 2100 Å. Pinder (*J.*, 1952, 2238) records ε 6700 at 2140 Å.

On ultra-violet irradiation in the presence of iodine, the morpholide polymerised a little but was not inverted. The new acid in ether gave no precipitate of relatively insoluble sorbic acid during 16 hours' irradiation but the residue from evaporation of the

solvent was substantially sorbic acid (m. p. 118—119°). Irradiation of pure sorbic acid gave a product with a similar low melting point, and this may be due to slight polymerisation or to production of a mixture of geometrical isomers in which sorbic acid predominates.

Configuration.—The long-known form of sorbic acid is undoubtedly *trans-trans*. This follows unambiguously from syntheses (*e.g.*, Doebner, *Ber.*, 1900, **33**, 2140; see von Auwers, *Annalen*, 1923, **432**, 46) and degradation experiments (*e.g.*, Doebner, *Ber.*, 1890, **23**, 2372; Heinänen, *Suomen Kem.*, 1938, *B*, **11**, 2), and is supported by *X*-ray diffraction data (Lonsdale, Robertson, and Woodward, *Proc. Roy. Soc.*, 1941, *A*, **178**, 43). [The formation of hexenolactone (II) as a by-product in the Doebner synthesis of sorbic acid (Joly and Amiard, *loc. cit.*) is probably due to lactonisation of the intermediate β-hydroxy-acid, followed by dehydration :

and not to intermediate production of *cis*-Δ^{α}-unsaturated acid.]

The new hexa-2 : 4-dienoic acid must therefore contain at least one *cis*-arrangement. The method of preparation indicated that it had the *cis*(αβ)-*trans*(γδ)-configuration (see Elvidge, Linstead, and Sims, *J.*, 1951, 3386). However, the acid could not readily be lactonised. With cold 75% sulphuric acid, boiling dilute acids, or on heating alone, only about 6% of neutral material was produced. The acid fractions contained unchanged starting material, polymer, or, on occasion, sorbic acid. The neutral fraction gave a positive Légal test and was therefore lactonic : no ketone was formed by hydrolysis with aqueous alkali, so that hex-2-eno-γ-lactone (I), which would have given 4-ketohexanoic acid, was not present. It seemed therefore that the product might be hex-2-eno-δ-lactone, though attempts to prove this were abortive. Hence other evidence to support the *cis-trans*-configuration of the new sorbic acid was sought.

Funke and Karrer (*Helv. Chim. Acta*, 1949, **32**, 1016) had converted methyl sorbate into *trans-trans*-muconaldehydic ester and we found that oxidation of the latter with silver oxide (cf. Wendler, Slater, Trenner, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 719) gave methyl hydrogen *trans-trans*-muconate in 18% yield. However, an attempt similarly to convert the methyl *cis-trans*-sorbate into a muconate failed at the first stage, ω-bromination with *N*-bromosuccinimide being accompanied by inversion.

We next examined elimination of the elements of water from the *cis*-hydroxy-acid (III). By treatment of the ethyl ester toluene-*p*-sulphonate (IV; R = Et, R′ = *p*-$C_6H_4Me{\cdot}SO_2$), or, better, the methanesulphonyl derivative of the methyl ester with cold aqueous alkali (cf. Linstead, Owen, and Webb, *J.*, 1953, 1211) the new isomeric sorbic acid was obtained. The *cis*-configuration about the αβ-double bond was thus directly shown, and additional good evidence provided for the *trans*-configuration about the γδ-double bond (see Elvidge, Linstead, and Sims, *loc. cit.*).

Bruylants and Rowies (*Bull. Soc. chim. Belg.*, 1951, **59**, 244) recently claimed the preparation of *cis-trans*-sorbic nitrile, and amide (m. p. 103°), in small yield *via* the condensation of cyanoacetic acid with crotonaldehyde, but no proof of configuration was given.

The action of sodium methoxide on the unsaturated γ-lactone (I) is very different from that on the δ-lactone. No *cis-trans*-sorbic acid was found—the product was almost entirely ketonic and some 4-ketohexanoic acid was isolated as the 2 : 4-dinitrophenylhydrazone. The lactone (I) is known to rearrange readily to the Δ^{β}-isomer (Lukeš, *Coll. Czech. Chem. Comm.*, 1929, **1**, 461). Presumably this occurs first, under the influence of the alkoxide, so that ring-opening to the enolate ion of the corresponding β-keto-ester follows. The esters of lævulic acids are very easily hydrolysed and the isolation of 4-ketohexanoic acid was presumably a result of the particular method of working. More complex ketonic material was present in the reaction mixture, presumably derived by alkoxide-induced self-condensation of the 4-keto-ester, but was not identified. The reaction of the lower homologue, Δ^{α}-angelicalactone, with sodium alkoxide is similarly complicated (Eskola, Udd, Leppänen, and Stjernvall, *Suomen Kem.*, 1947, *B*, **20**, 13) and apparently yields bimolecular condensation products of *cyclo*pentane-1 : 3-dione.

Experimental

Hex-2-eno-δ-lactone (II) (*Racemic δ-Methyl-Δ$^{\alpha}$-pentenolide*).—*Method* (i). This (Haynes and Jones, *loc. cit.*) gave a lactone of m. p. 12·8—13·5°, b. p. 102·5—103°/12 mm., n_D^{18} 1·4710 (Found: C, 64·4; H, 7·3. Calc. for $C_6H_8O_2$: C, 64·3; H, 7·2%).

Method (ii). Hydrobromic acid (400 c.c.; *d* 1·45) was treated with dry hydrogen bromide until 170 g. had been absorbed. Finely powdered sorbic acid (87 g.) was added, and the mixture agitated and treated further with hydrogen bromide at intervals during 7 weeks, after which 2 : 5-dibromohexanoic acid (92 g.), m. p. 45—52°, was collected. According to Kuhn and Jerchel's method (*loc. cit.*), this acid (30 g.) and water (350 c.c.) were heated under reflux for 2—3 hours. Extraction with ether and distillation gave the following fractions at 13 mm.: (*a*) b. p. 106—107°, n_D^{23} 1·4700; (*b*) 108—109°, n_D^{23} 1·4700; (*c*) 109—112°, n_D^{23} 1·4710; (*d*) 112—116°, n_D^{23} 1·4721. When cooled to 0° and seeded with the solid lactone from method (i), fractions (*a*), (*b*), and (*c*) solidified. The solid had m. p. 11·5° undepressed by the preceding preparation.

Reaction with boiling sodium hydroxide. The lactone (II) (106 mg.) was treated with boiling 30% sodium hydroxide (4 c.c.) for 50 min. The solution was cooled, acidified, and chilled in ice, and the *trans-trans*-sorbic acid collected (69·5 mg., 65%). Crystallised from water it had m. p. 128—130°, undepressed by authentic material.

Reaction with barium hydroxide. The lactone (II) (1 g.) and saturated barium hydroxide solution (27 c.c.) were heated on the steam-bath for 2·5 hours. The cooled solution was treated with carbon dioxide, and the filtrate concentrated under reduced pressure to 15 c.c. *S*-Benzylthiuronium chloride (3 g.) in water was added. S-*Benzylthiuronium* 5-*hydroxyhex*-cis-2-*enoate* (1·55 g.) formed needles, m. p. 116—117°, from ethyl acetate (Found: C, 56·4; H, 6·9; N, 9·3. $C_{14}H_{20}O_3N_2S$ requires C, 56·7; H, 6·8; N, 9·45%).

5-*Hydroxyhex*-cis-2-*enoic Acid* (III).—Hex-2-eno-δ-lactone (II) (1 g.) and N-potassium hydroxide (10 c.c.) were heated on the steam-bath for 5 min. The solution was cooled in ice, acidified with 2N-sulphuric acid (5 c.c.) and extracted 5 times with ether, the temperature being kept at 0°. The ethereal extracts were washed twice with water, dried ($MgSO_4$), and evaporated under reduced pressure (at room temp.), 5-hydroxyhex-*cis*-2-enoic acid (1·01 g.) being left as an oil (Found, by titration with 0·05N-NaOH: equiv., 155. Calc. for $C_6H_{10}O_3$: equiv., 130. Therefore, purity = 84%). Hexenolactone did not react with 0·05N-sodium hydroxide under similar conditions.

The acid (0·168 g.) in ether was treated with a solution of cinchonidine (0·3 g.) in acetone. After several days, crystals of the cinchonidine *salt* separated as needles, which after several crystallisations from acetone had m. p. 133·5—134·5° (Found: N, 6·6. $C_{25}H_{32}O_4N_2$ requires N, 6·6%).

Methyl 5-*Hydroxyhex*-cis-2-*enoate* (VI; R = Me).—(*a*) 5-Hydroxyhex-*cis*-2-enoic acid (from hexenolactone, above) in ether was treated with ethereal diazomethane, the solvent evaporated under reduced pressure, and the methyl 5-hydroxyhex-*cis*-2-enoate distilled; it had b. p. 62—64°/0·5 mm., n_D^{23} 1·4592, and was characterised as the 3 : 5-*dinitrobenzoate*, which crystallised from methanol as pale yellow prisms, m. p. 86—87° (Found: N, 8·3. $C_{14}H_{14}O_8N_2$ requires N, 8·3%).

(*b*) 5-Hydroxyhex-2-ynoic acid (Haynes and Jones, *J.*, 1946, 503) was heated overnight under reflux with methanol (10 vols.) containing 1% of sulphuric acid, and the neutral product distilled to yield *methyl* 5-*hydroxyhex*-2-*ynoate*, b. p. 83°/0·12 mm., n_D^{22} 1·4680 (Found: C, 58·6; H, 7·1. $C_7H_{10}O_3$ requires C, 59·15; H, 7·1%). A portion (740 mg.) in methyl acetate (40 c.c.) was semihydrogenated (allowed hydrogen uptake: 120 c.c. at 766 mm./23°) over 2% palladium–strontium carbonate. The derived 3 : 5-dinitrobenzoate had m. p. 85—87° alone and when mixed with the previous preparation.

cis-trans-*Sorbic Acid.*—(*a*) Hexenolactone (II) (3·2 g., 1 mol.) was kept with a solution of sodium (0·66 g., 1 mol.) in methanol (100 c.c.) for 30 min. The solvent was distilled off under reduced pressure, the residue dissolved in water, and the solution washed with ether and acidified with hydrochloric acid. The solution was extracted 3 times with ether, the ethereal extracts were washed with water, dried ($MgSO_4$), and evaporated. The residual oil (2·49 g., 78%) crystallised slowly at 0°, and was recrystallised from pentane (by cooling to —70°), affording needles of cis-trans-*sorbic acid*, m. p. 32—35° (Found: C, 64·4, H, 7·4%; equiv., 112. $C_6H_8O_2$ requires C, 64·3; H, 7·2%; equiv., 112). The acid distilled unchanged under reduced pressure and had b. p. 121—125°/16 mm. It polymerised during 2—3 hours at room temperature, but much more slowly at 0°, to a clear brittle resin.

The S-*benzylthiuronium* salt, prepared in water, crystallised from ethyl acetate (rapidly, to avoid decomposition) as needles, m. p. 137° (Found: N, 9·9. $C_{14}H_{16}O_2N_2S$ requires N, 10·1%).

(*b*) Hexenolactone (II) (5·6 g.) was treated with methanolic sodium methoxide (from 1·15 g. of sodium). The acidic fraction afforded *cis-trans*-sorbic acid (4·0 g., 71%). From the neutral fraction, methyl *cis-trans*-sorbate (see below) was obtained which after two distillations had b. p. 80°/21 mm., n_D^{21} 1·4944. Light absorption in ethanol: max. at 2510, 2570 Å; ε = 18,300, 21,800.

Derivatives of cis-trans-*Sorbic Acid.*—*cis-trans*-Sorbic acid and diazomethane in ether gave, after two distillations of the product, *methyl* cis-trans-*sorbate*, b. p. 60°/11 mm., n_D^{23} 1·4948 (Found: C, 66·0; H, 8·0. $C_7H_{10}O_2$ requires C, 66·6; H, 8·0%).

To a solution of the acid (2·2 g.) in pentane at 0°, oxalyl chloride (2·2 c.c.) and pyridine (1 drop) were added. After 2·5 hours at room temperature and 1 hour at 35—40°, the solution was evaporated under reduced pressure. Dry ether was distilled from the residue, which was then dissolved in benzene and treated at 0° with gaseous ammonia. The solution was filtered, and the solid repeatedly extracted with boiling ethyl acetate. Evaporation of the combined extracts and filtrate afforded cis-trans-*sorbamide* (1·47 g.) which after several crystallisations from ethyl acetate–light petroleum (b. p. 60—80°) and sublimation at 100°/20 mm. had m. p. 113—114° (Found: N, 12·5. C_6H_9ON requires N, 12·6%).

cis-trans-Sorbic acid (0·55 g.) was converted into its acid chloride as above and the ethereal solution treated with benzylamine (1·1 g.) in ether (10 c.c.) at 0°. After 1 hour, the solution was washed successively with water, 2N-sulphuric acid, aqueous sodium hydrogen carbonate, and water, and dried ($MgSO_4$), and the ether distilled off. N-*Benzyl*-cis-trans-*sorbamide* (0·88 g.) crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 82—83° (Found: N, 7·2. $C_{13}H_{15}ON$ requires N, 7·0%).

The *morpholide*, prepared similarly, was an oil, b. p. *ca.* 115°/0·5 mm., n_D^{23} 1·5451 (Found: N, 7·6. $C_{10}H_{15}O_2N$ requires N, 7·7%).

The iso*butylamide* was obtained as an oil which after two distillations at 90°/0·1 mm. solidified and had m. p. 33—35° (Found: N, 8·1. $C_{10}H_{17}ON$ requires N, 8·4%).

Derivatives of trans-trans-*Sorbic Acid.*—The S-*benzylthiuronium* salt crystallised from methanol–ether as laths, m. p. 169—170° (Found: C, 60·4; H, 6·6. $C_{14}H_{18}O_2N_2S$ requires C, 60·4; H, 6·5%).

The amide prepared from the acid *via* the acid chloride had m. p. 168—169° after crystallisation from water or ethyl acetate. Doebner and Wolff (*Ber.*, 1901, **34**, 2221) give m. p. 168°.

The *benzylamide* crystallised from benzene in needles, m. p. 130·5—131·5° (Found: N, 7·1. $C_{13}H_{15}ON$ requires N, 7·0%).

The *morpholide* crystallised from light petroleum (b. p. 60—80°) in silky needles, m. p. 75—76° (Found: N, 7·6. $C_{10}H_{15}O_2N$ requires N, 7·7%). It polymerised rapidly at room temperature, more slowly at 0°.

2 : 3-*Dihydro*-2-*methyl*-6-*pyridone* (VII).—The lactam (Fischer and Schlotterbeck, *loc. cit.*), after several crystallisations from ethyl acetate–light petroleum (b. p. 60—80°) and sublimation at 100°/20 mm., had m. p. 105·5—106°. A mixture with *cis-trans*-sorbamide had m. p. 75—80°.

Oxidation of the Lactam.—The lactam (0·55 g.) in water (40 c.c.) was treated with potassium permanganate (2·1 g., 4O) in water (150 c.c.) at 0° (stirring), the solution was decolorised (Na_2SO_3), boiled, and filtered, and the filtrate extracted continuously with ether, to yield N-(1-*carboxy*-2-*propyl*)*oxamic acid* (VIII) (0·75 g.), which crystallised from ethyl acetate–light petroleum (b. p. 60—80°) as needles, m. p. 156—157° (decomp.) (Found: N, 7·5. $C_6H_9O_5N$ requires N, 8·0%). The acid (0·33 g.) and 10% aqueous sodium hydroxide were boiled under reflux for 2 hours, and the solution was acidified and filtered. The filtrate was heated to boiling, treated with aqueous calcium chloride (0·5 g.), and neutralised with 2N-ammonia. The precipitated calcium oxalate (0·223 g., 80%) was treated with hydrochloric acid and continuously extracted with ether, affording oxalic acid, m. p. 185° (decomp., with softening at 95—100°) undepressed by an authentic specimen.

Hydrogenation of cis-trans-*Sorbic Acid.*—The acid (7 mg.) in ethanol in the presence of Adams's catalyst absorbed 1·55 mols. of hydrogen. The filtered solution was neutralised with dilute aqueous sodium hydroxide, concentrated to small volume under reduced pressure, and treated with *S*-benzylthiuronium chloride (20 mg.) in water. The precipitated solid had m. p. 146—147°, undepressed in admixture with S-*benzylthiuronium hexanoate*, which crystallised from ethanol in laths, m. p. 149·5—150° (Found: N, 9·8. $C_{14}H_{22}O_2N_2S$ requires N, 9·9%).

Hydrogenation of cis-trans-*Sorbamide.*—The amide (448 mg.) in ethanol (10 c.c.) was hydrogenated in the presence of Adams's catalyst (30 mg.) (uptake of hydrogen: 210 c.c. at 21°/772

mm. Calc. for 2 mols. : 192 c.c.). Evaporation of the filtered solution under reduced pressure and crystallisation of the residue from water afforded hexanoamide, m. p. 98—99° undepressed by authentic material.

Oxidation of cis-trans-*Sorbamide.*—The amide (810 mg.) in water (50 c.c.) was treated with a solution of potassium permanganate (6·32 g.; 8O) in water (200 c.c.) at 0° with stirring. The solution was filtered, decolorised with sodium sulphite, boiled to coagulate manganese dioxide, and filtered. The filtrate was acidified with acetic acid, heated to boiling, and treated with a hot solution of calcium chloride (0·8 g.) in water. After addition of 2N-ammonia, the mixture was allowed to cool, and the precipitated calcium oxalate collected (filtrate *A*), washed, and dried (yield, 384 mg.). Addition of aqueous hydrochloric acid to the salt, followed by continuous ether-extraction, afforded oxalic acid (156 mg.), which after crystallisation from ethyl acetate–light petroleum (b. p. 60—80°), had m. p. 100° with resolidification and then m. p. 183—184° (decomp.), undepressed by an authentic specimen. The filtrate *A* from the calcium oxalate was continuously extracted with ether for 20 hours. Evaporation of the ether afforded oxamic acid (203 mg.) which after one crystallisation from water had m. p. 202—204° (decomp.).

Inversion Experiments with cis-trans-*Sorbic Acid and its Derivatives.*—(a) *Boiling water. cis-trans*-Sorbic acid (24 mg.) and water (2·5 c.c.) were heated under reflux for 20 min. Evaporation of the solution in a desiccator afforded crystals of unchanged starting material, identified by m. p. and conversion into the *S*-benzylthiuronium salt.

(b) *Sodium hydroxide.* (i) The acid (0·2 g.) was boiled in 30% sodium hydroxide solution (7·5 c.c.) under reflux for 1·3 hours, cooled, acidified, chilled in ice, and filtered. The *trans-trans*-sorbic acid (yield, quantitative) was crystallised from water (charcoal), and then had m. p. 131—132° undepressed by authentic material. (ii) The *cis-trans*-acid (0·1 g.) in 30% sodium hydroxide solution (4 c.c.) was kept for 7 weeks in the dark at room temperature. The solution was acidified at 0° and the precipitated acid (50 mg.) recrystallised from water; it then had m. p. 123—126° undepressed by *trans-trans*-sorbic acid. (iii) *cis-trans*-Sorbamide (34 mg.) and 30% sodium hydroxide solution (2 c.c.) were heated under reflux for 1 hour. Acidification of the cooled solution precipitated an acid with m. p. 127—129°, undepressed by *trans-trans*-sorbic acid.

(c) *Irradiation. cis-trans*-Sorbic acid (21 mg.) in dry ether (1 c.c.) containing a trace of iodine was irradiated with ultra-violet light from a Hanovia lamp for 16 hours. The solution was evaporated under reduced pressure, and the residual solid acid (m. p. 100—105°) recrystallised twice from carbon tetrachloride. It then had m. p. 118—119°, and m. p. 122—124° when mixed with *trans-trans*-sorbic acid.

(d) Irradiation of the *cis-trans*-morpholide under similar conditions effected no appreciable change [Found, for recovered material : $n_D^{22\cdot5}$ 1·5452; light adsorption in ethanol, max. at 2510, 2580, 2640 Å (ε = 15,400, 17,000, 17,000)].

Irradiation of *trans-trans*-sorbic acid under similar conditions yielded material with m. p. 114—118°, raised to 117—120° after one crystallisation from carbon tetrachloride.

Lactonisation Attempts.—(*a*) *cis-trans*-Sorbic acid (1 g.) and water (10 c.c.) containing hydrochloric acid (3 drops) were heated under reflux for 12 hours. The cooled solution was made alkaline (Na_2CO_3) and extracted with ether. Evaporation of the extract afforded an oil (50 mg.) which gave a positive Légal test. From the alkaline aqueous phase, by acidification and ether-extraction, unchanged starting material (0·6 g.) was recovered, identified as the *S*-benzylthiuronium salt.

(*b*) *cis-trans*-Sorbic acid (1 g.) was heated at 154° for 2·5 hours and the product shaken with 2N-sodium carbonate and ether. From the aqueous phase unchanged starting material (0·55 g.) was recovered, identified as above. Evaporation of the ether afforded an oil (0·1 g.) which gave a positive Légal test, but no precipitate was obtained with aqueous 2 : 4-dinitrophenylhydrazine hydrochloride after alkaline hydrolysis of a portion. Derivation of a salt of (III) from the oil was not achieved.

Oxidation of trans-trans-*Muconaldehydic Methyl Ester.*—The ester aldehyde (Funke and Karrer, *loc. cit.*) (115 mg.; purified by sublimation at 100°/20 mm.) in methanol (5 c.c.) was shaken for 2 days with an alkaline suspension of silver oxide, made by treating silver nitrate (0·5 g.) in water (5 c.c.) with potassium hydroxide (175 mg.) in 95% methanol (7·5 c.c.). The mixture was filtered, and the residue washed with water (100 c.c.) and the filtrate with ether. The aqueous layer was acidified (HCl), and methyl hydrogen *trans-trans*-muconate (18·5 mg.), m. p. 161—162°, isolated with ether.

ω-*Bromination of Methyl* cis-trans-*Sorbate.*—The ester (12·53 g.), carbon tetrachloride (1 c.c.), and *N*-bromosuccinimide (5·85 g., 0·33 mol.) were heated at 120—130° for 30 min. (cf.

Heilbron, Jones, and O'Sullivan, *J.*, 1946, 866). Milder conditions were ineffective. Fractionation of the liquid product gave (i) methyl *trans-trans*-sorbate (8·7 g.), b. p. 60—63°/10 mm., n_D^{18} 1·5012—1·5027, characterised by conversion into the benzylamide, and (ii) crude methyl ω-bromo-*trans-trans*-sorbate (0·83 g.), b. p. 73—77°/0·1 mm., n_D^{18} 1·5263, and 0·36 g., b. p. 77—83°/0·1 mm., n_D^{18} 1·5321. Fraction (ii) (100 mg.), potassium phthalimide (100 mg.), and dry methanol (2 c.c.) were heated under reflux for 2 hours (cf. Karrer and Schwyzer, *Helv. Chim. Acta*, 1946, **29**, 1191). On cooling of the solution to 0°, methyl ω-phthalimido-*trans-trans*-sorbate (28 mg.) crystallised, having m. p. 150—152° undepressed by a specimen prepared from authentic methyl ω-bromo-*trans-trans*-sorbate, b. p. 80°/0·5 mm., n_D^{21} 1·5409.

Dehydration of 5-*Hydroxyhex*-cis-2-*enoic Acid: Formation of* cis-trans-*Sorbic Acid.*—(*a*) Ethyl 5-hydroxyhex-*cis*-2-enoate (Haynes and Jones, *J.*, 1946, 954) (3 g.) in pyridine (5 c.c.) was added at 0° to a pyridine solution (5 c.c.) of toluene-*p*-sulphonyl chloride (3·6 g.). The mixture was kept at 0—2° overnight, and ice-water then added. The solution was extracted 4 times with chloroform, and the extract washed with dilute sulphuric acid, aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and evaporated. The crude oily toluenesulphonyl derivative was stirred with N-potassium hydroxide (50 c.c.) for 6 days, and the oily acidic fraction (1·21 g.) subsequently isolated with ether. The pentane-soluble fraction was dissolved in water, and the solution neutralised with dilute aqueous sodium hydroxide. The derived *S*-benzylthiuronium salt had m. p. 139—140°, undepressed in admixture with the salt of *cis-trans*-sorbic acid obtained above.

(*b*) Methyl 5-hydroxyhex-*cis*-2-enoate (3·43 g.) in dried pyridine (3 c.c.) was treated at 0° with methanesulphonyl chloride (2 c.c.) in pyridine (3 c.c.), and the crude derivative stirred with N-potassium hydroxide (90 c.c.) overnight. Isolation as before with ether and extraction with pentane afforded an oil (0·62 g., 23%) which slowly crystallised. Recrystallisation from pentane (at −70°) afforded *cis-trans*-sorbic acid, m. p. 28—31°. The *S*-benzylthiuronium salt had m. p. and mixed m. p. 140—141°.

Action of Sodium Methoxide.—Δ^{α}-Homoangelicalactone (I) (racemic γ-ethyl-Δ^{α}-butenolide), prepared according to Kuhn and Jerchel (*loc. cit.*), had b. p. 99—100°/19 mm., n_D^{22} 1·4561. The lactone (I) (3·69 g.) was dissolved in ice-cold methanolic sodium methoxide (100 c.c.; from 0·76 g. of sodium), the solvent at once removed under reduced pressure (without heating), and the residue dissolved in water. The solution was acidified, extracted with ether several times, and the ether back-extracted with 2N-sodium carbonate. Isolation from the acidified aqueous phase with ether afforded an oil (2·6 g.), which was extracted with pentane: at −70° the extract remained clear and did not deposit *cis-trans*-sorbic acid. The pentane-insoluble fraction (0·65 g.), in acetic acid (25 c.c.) with 2 : 4-dinitrophenylhydrazine, gave a dinitrophenylhydrazone (0·24 g.) and filtrate *B*. After crystallisation from ethyl acetate, the derivative had m. p. 186° alone and when mixed with 4-(2 : 4-*dinitrophenylhydrazono*)*hexanoic acid*, which formed needles, m. p. 187—189°, from benzene or ethyl acetate (Found: N, 18·1. $C_{12}H_{14}O_6N_4$ requires N, 18·0%). Authentic 4-ketohexanoic acid was prepared in 26% yield from diethylcadmium and succinic anhydride (cf. de Benneville, *J. Org. Chem.*, 1941, **6**, 462).

By concentration of the filtrate *B*, a second *derivative* (0·66 g.) was separated, which after crystallisation from ethyl acetate had m. p. 193° (Found: C, 41·35; H, 3·6; N, 21·8, 22·9%). The m. p. was depressed to 160° by the above dinitrophenylhydrazone.

Analyses were carried out in the microanalytical laboratory (Mr. F. H. Oliver), and measurements of ultra-violet light absorption in the spectrographic laboratory (Mrs. A. I. Boston) of this Department. The infra-red absorption data and insecticidal test results were obtained through the courtesy of Dr. L. Crombie. Grateful acknowledgment is made to the Department of Scientific and Industrial Research for a maintenance grant (to U. E.).

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282. *The Oxidation of Hydrazine in Aqueous Solution. Part I. The Nature of 1- and 2-Electron-transfer Reactions, with Particular Reference to the Oxidation of Hydrazine.*

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The classification of oxidising agents as 1- or 2-electron-transfer reagents, depending on the products of their reaction with hydrazine, is discussed and further evidence is presented. A new empirical criterion is suggested and its implications in terms of the reaction mechanism are considered. The more detailed nature of 1- and 2-electron transfer reactions is discussed.

In one of the earliest papers in which 1- and 2-electron-transfer reactions were distinguished, Kirk and Browne (*J. Amer. Chem. Soc.*, 1928, **50**, 337, *q.v.* for references) discussed the implications of previous work on the oxidation of hydrazine, and common features of the reaction of a large number of oxidising agents with hydrazine were pointed out (for a review see also Audrieth and Ogg, "The Chemistry of Hydrazine," John Wiley and Sons, Inc., New York, 1951, Chap. VI). They conclude: "The hitherto unaccountable similarity in the behaviour of various oxidants of widely divergent potentials towards hydrazine is now explained on the ground that they are *mono-delectronators* yielding ammonia as the only by-product of the reaction, or *di-delectronators* yielding both ammonia and hydronitric acid." (The main product of the reaction is nitrogen gas.) Hydrazoic acid formation in boiling, strongly acid solution containing excess of hydrazine thus becomes a criterion for the presence of a 2-electron-transfer oxidising agent. Departure from the rather critical reaction conditions can lead to a great diminution in the yield of hydrazoic acid or even to its disappearance.

Although Kirk and Browne stated that positive and negative ions are included in each class, we noticed that, of the reagents to which they referred specifically, all the simple metal ions fell into the one class while oxy-acids and their salts, and uncharged oxidising agents such as hydrogen peroxide, belonged to the other, giving hydrazoic acid as a reaction product. Thus an alternative distinction could be between reagents able or unable to form a co-ordinate complex of the type $Ox \leftarrow NH_2 \cdot NH_2(H^+)$. In an attempt to decide the true basis for the classification we have determined the products of oxidation by the hydroxyl radical and by the thallic ion. Each of these falls into a different class depending on whether it is considered as a 1- or 2-electron-transfer reagent, or as a non-complex-forming or a complex-forming oxidising agent respectively.

Experimentally, oxidation by the hydroxyl ion is much easier to carry out in cold solutions than in the boiling solutions necessary for the formation of hydrazoic acid. Also, solutions containing thallic ion are often unstable when hot. However, as the annexed Table shows, a grouping similar to Kirk and Browne's is obtained if distinction is made between (*a*) reagents which oxidise hydrazine at room temperature in acid solution to nitrogen and water only, irrespective of the order of addition, and (*b*) other reagents which under similar conditions yield nitrogen and ammonia in variable quantities. The number of equivalents of the latter class of reagents consumed per molecule of hydrazine is always lower than 4 and varies to some extent with the manner of mixing. For the former reagents, which correspond to those which form hydrazoic acid in boiling acid solution, 4 equivalents of oxidising agent are consumed. Except where stated, the results quoted are from the previous work to which reference is made above, though we have checked most of the stoicheiometries. The behaviour of the hydroxyl radical and thallic ion, neither of which has previously been examined as an oxidising agent for hydrazine, leads us to believe that Kirk and Browne's classification into 1- and 2-electron-transfer reagents is correct.

Our criterion cannot be applied in as many cases as Kirk and Browne's since several reagents, notably salts of oxy-acids, which react at higher temperatures, do not react at all at room temperature. We consider Kirk and Browne's conclusions to be unsatisfactory for several oxidising agents; hydrogen peroxide and potassium peroxy-

disulphate are important examples since these reagents give rise to the highest reported yields of hydrazoic acid (Browne and Shetterly, *J. Amer. Chem. Soc.*, **1909**, **31**, 783). However, Davis (Thesis, Manchester Univ., 1951), using small amounts of ethylenediaminetetra-acetic acid (disodium salt) to sequester heavy-metal ions, has shown that

Reagent	Stoicheiometry (cold)	HN_3 (cold)	HN_3 (hot)	Remarks
Ce(IV)	1·05—1·4	+	—	
Fe(III)	1·1—1·35	+	—	Very slow reaction at 25°; higher stoicheiometries in hot soln.
Mn(III)	1·09—1·47	+	—	Complex acetate
OH	1·07—1·96	+	N.I.	See Exptal. section
I_2	4	—	—	Very slow reaction at 25°; HIO?
Br_2	4	—	+	
Cl_2	N.I.		+	
KIO_3	4	—	—	
$KBrO_3$	4	—	+	Needs high HCl concn. for quant. reaction in cold
$KClO_3$	No reaction		+	
$K_2S_2O_8$ ...	No reaction		+	Reactive species in hot solution doubtful
H_2O_2	No reaction		+	,, ,, ,,
Tl(III)	4	—	+	See Exptal. section ,, ,,
$K_2Cr_2O_7$ ...	3—4	+	+	1- and 2-Electron-transfer possible
V(V)	3·5—4	+	+	,, ,, ,,
$KMnO_4$ ...	1·45—2·2	+	+	,, ,, ,,

N.I. = Not investigated.

reaction between hydrazine and hydrogen peroxide in aqueous solution at 25° is catalysed by traces of metal ions even if " pure " reactants are used, and that there is no good evidence for a direct reaction. Under conditions similar to those used in hydrazoic acid formation he concluded that the catalysed reaction predominates. Since it is possible that the formation of hydrazoic acid is due to the oxidation of hydrazine by a metal-ion intermediate and not by hydrogen peroxide itself, Kirk and Browne's classification of hydrogen peroxide as a 2-electron-transfer oxidising agent in this reaction is of doubtful value. In the case of potassium peroxydisulphate there is some evidence for trace-metal catalysis unless the reagents are reasonably pure. Kolthoff and Miller's work at higher temperatures (*J. Amer. Chem. Soc.*, 1951, **73**, 3055) makes it probable that reaction occurs in the absence of heavy-metal ions, but whether peroxydisulphate or one of its decomposition products reacts with the hydrazine would be difficult to decide.

Kirk and Browne suggested that the halogens may act either as 1- or 2-electron-transfer reagents and actually referred to iodine as a " mono-delectronator." 1-Electron-transfer oxidation by any of these reagents seems unlikely for reactions with a non-metallic substrate, and in dilute acid conditions bromine and iodine lead to quantitative formation of nitrogen. The form in which iodine reacts is uncertain, for Berthoud and Porret's interpretation of the kinetics of the oxidation in acid solution is that hypoiodous acid is the reactive species (*Helv. Chim. Acta*, 1934, **17**, 32).

Previous workers attempted to explain the different products obtained with 1- and 2-electron-transfer reagents in terms of the reactions of the various radicals which it was assumed could be formed in the initial processes. The reaction schemes below which we consider explain the different behaviour of 1- and 2-electron-transfer reagents in cold, acid solution are simpler than those developed previously (see Audieth and Ogg, *op. cit.*, p. 128). In agreement with the earlier mechanisms we depict hydrazine and the derived radicals as possessing zero charge. Almost certainly this is not always the case, but there is no evidence necessitating that the radicals should react in a particular form, and there is little evidence about hydrazine itself. The formulæ used therefore merely represent the oxidation state of the nitrogen atoms concerned and not the detailed structure of the radical. We suggest that the quantitative oxidation of hydrazine to nitrogen by 2-electron-transfer reagents is in accord with the scheme

$$N_2H_4 \xrightarrow[-(2e)]{} N_2H_2 \dashrightarrow N_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

in which N_2H_2, once formed, can lead to nitrogen but not to ammonia. Whether the N_2H_2 becomes nitrogen through further oxidation or by a disproportionation reaction between

two such radicals giving nitrogen and hydrazine is immaterial for our present purpose. The variable stoicheiometry obtained with the 1-electron-transfer reagents results from two competing reactions which can follow the initial formation of N_2H_3:

$$N_2H_4 \xrightarrow{-(e)} N_2H_3 \begin{cases} \xrightarrow{\text{Dimerisation}} \tfrac{1}{2}N_4H_6 \dashrightarrow \tfrac{1}{2}N_2 + NH_3 & (2a) \\ \xrightarrow{-(e)} N_2H_2 \dashrightarrow N_2 & (2b) \end{cases}$$

Reaction (2*a*) leads to a stoicheiometry of 1, and (2*b*) to stoicheiometry of 4; so the stoicheiometry for 1-electron-transfer reagents may lie between 1 and 4 depending on the proportion of these two reactions. In alkaline solution even 1-electron-transfer reagents produce nitrogen quantitatively. The effect of the large change in hydrogen-ion concentration must therefore be to increase greatly the rate of oxidation of N_2H_3 relatively to the dimerisation. (For similar mechanisms, otherwise interpreted, see Cuy and his collaborators, *J. Amer. Chem. Soc.*, 1924, **46**, 1796, 1810.)

For reaction with 1-electron-transfer reagents, equations (2*a*) and (2*b*) predict that the consumption of oxidising agent per mole of hydrazine will be lower if the hydrazine is kept in excess than if the oxidising agent is kept in excess. This we have observed, especially with ceric sulphate, ferric sulphate, and potassium permanganate. The last is not, strictly, a 1-electron-transfer reagent but a complex oxidising agent in that the change in acid solution of the valency state of the manganese from (VII) to (II) probably involves both 1- and 2-electron-transfer reactions. This and similar oxidising agents therefore have some of the properties of both the simple types of oxidising agent. Thus in acid solution less than 4 equivalents of potassium permanganate are consumed and the stoicheiometry can be varied by altering the conditions of mixing. On the other hand, small quantities of hydrazoic acid are produced if reaction is carried out with hot solutions. The products of the oxidation of hydrazine by complex electron-transfer reagents, like those of 1-electron-transfer reagents, can be expressed in terms of two limiting overall reactions which take place simultaneously: $N_2H_4 - (e) \longrightarrow \frac{1}{2}N_2 + NH_3$, and $N_2H_4 - 4(e) \longrightarrow N_2$. The proportion in which these occur determines the stoicheiometry. In practice the 1-electron-transfer reagents generally have stoicheiometries fairly near to 1, and the complex reagents, probably because of the occurrence of 2-electron-transfer steps, nearer to 4.

Detailed Nature of Electron-transfer Reactions.—1- and 2-Electron-transfer reactions may be defined as processes in which two species change their oxidation number by one or two units respectively in one kinetic step. An electron-transfer reaction, even between two metal ions, can almost always be represented as an atom- or radical-transfer reaction as well as a process involving the actual transfer of electrons. For example, compare the alternative schemes by which three different types of reaction may be represented:

(i) $HO + N_2H_4 \longrightarrow HOH + N_2H_3$

or $HO + N_2H_4 \longrightarrow HO^- + N_2H_4^+ \longrightarrow HOH + N_2H_3$

(ii) $Fe^{++} + HO{\cdot}OH \longrightarrow (Fe \cdots \overset{H}{O} \cdots OH)^{++} \longrightarrow FeOH^{++} + OH$

or $Fe^{++} + HO{\cdot}OH \longrightarrow Fe^{+++} + (HO{\cdot}OH)^- \longrightarrow Fe^{+++} + HO^- + OH$

(iii) $Fe^{+++} + Cl^- + Ti^{+++} \longrightarrow FeCl^{++} + Ti^{+++} \longrightarrow (Fe \cdots Cl \cdots Ti)^{5+} \longrightarrow Fe^{++} + TiCl^{+++} \longrightarrow Fe^{++} + Cl^- + Ti^{4+}$

or $Fe^{+++} + Ti^{+++} \longrightarrow Fe^{++} + Ti^{4+}$

For these and other 1-electron-transfer reactions in solution there seems to be no certainty as to the actual mechanism, and the term " electron-transfer reaction " as usually employed should merely be taken to mean an oxidation–reduction reaction. In the few cases where evidence is available, the reaction does not involve the transfer of electrons; thus Halperin and Taube have shown that oxygen-atom transfer occurs in the oxidation of sulphite to sulphate by chlorate (*J. Amer. Chem. Soc.*, 1950, **72**, 3319). Such a reaction is a clear example of a 2-electron-transfer reaction (in its usual sense) occurring in a simple process. In the same way, oxidation of hydrazine by iodate may occur by oxygen-atom transfer

from IO_3^- or IO_2^+ (see Morgan, Peard, and Cullis, *J.*, 1951, 1865) and this may also be true of the reaction with other oxy-acids.

The oxidation by Tl(III) may involve a similar process, but may on the other hand involve the series

$$Tl(III) + N_2H_4 \longrightarrow Tl(II)\cdot N_2H_3 \longrightarrow Tl(I)\cdot N_2H_2 \longrightarrow Tl(I) + N_2H_2$$

in which a single 1-electron-transfer oxidation forms Tl(II) in the vicinity of N_2H_3. Before these two can separate, Tl(II), which must be a stronger oxidising agent than Tl(III), is able to oxidise N_2H_3, a stronger reducing agent than N_2H_4, to N_2H_2. The reaction of V(V) with hydrazine emphasises this distinction. V(V) is reduced by hydrazine in acid solution to V(IV), and between 3·5 and 4 V(V) ions are reduced per hydrazine molecule oxidised. This compares with the stoicheiometries between 1 and 1·5 observed with Ce(IV), Fe(III), and Mn(III). We therefore suggest that the predominant reaction with V(V) is $V(V) + N_2H_4 \longrightarrow V(III) + N_2H_2$. The reaction $V(V) + V(III) \longrightarrow 2V(IV)$ then occurs rapidly; the appropriate redox potentials are; $V(V)/V(IV) = 1{\cdot}00$, $V(IV)/V(III) = 0{\cdot}36$. (Redox potentials quoted have generally been taken from Latimer, "The Oxidation States of the Elements and their Potentials in Aqueous Solutions," Prentice-Hall Inc., New York, 2nd Edn., 1952.) The overall reaction thus approximates to $4V(V) + N_2H_4 \longrightarrow 4V(IV) + N_2$. Kirk and Browne (*loc. cit.*) have shown that V(III) is formed in the reaction mixture when hot, and also that hydrazoic acid can be formed. The comparatively small quantity of ammonia produced at room temperature, implying the formation of small quantities of N_2H_3, can be interpreted in two ways: either there can be two distinct reactions between V(V) and N_2H_4, *viz.*, $V(V) + N_2H_4 \longrightarrow V(III) + N_2H_2$ and $V(V) + N_2H_4 \longrightarrow V(IV) + N_2H_3$, of which the former predominates; or the reaction can be written:

$$V(V) + N_2H_4 \longrightarrow V(IV)\cdot N_2H_3 \begin{cases} \longrightarrow V(III) + N_2H_2 \\ \longrightarrow V(IV) + N_2H_3 \end{cases}$$

The second possibility corresponds to the two-stage mechanism suggested for oxidation by Tl(III), but here the intermediate form, V(IV), is a much less powerful oxidising agent than Tl(II) (redox potential $Tl(II)/Tl(I) > 1{\cdot}25$) and hence a small proportion of the $V(IV)\cdot N_2H_3$ complexes may dissociate before the subsequent oxidation to N_2H_2 takes place.

We consider that in the oxidation of hydrazine by 2-electron-transfer reagents the single-stage type of mechanism is the more probable. It is very likely to occur when oxy-acids bring about oxygen-atom transfer, and the following considerations make it probable with metal-ion 2-electron-transfer oxidising agents. If the two-stage mechanism is correct we should expect the rate of reaction to be determined by the first stage only, since the second stage is virtually an independent reaction: one would then expect a parallel between the rates of reaction of the similar ions of Fe(III) and Tl(III) with hydrazine, and the corresponding redox potentials of Fe(III)/Fe(II) and Tl(III)/Tl(II). The latter potential cannot be measured, but from the slow reaction between Tl(III) and Fe(II) in perchloric acid solution (Johnson, *J. Amer. Chem. Soc.*, 1952, **74**, 959) which has been shown to involve a rate-determining 1-electron-transfer reaction between these two species (Ashurst and Higginson, unpublished work) we estimate that it is not greater than the potential of Fe(III)/Fe(II). Though the redox potentials are similar, the rate of reaction of hydrazine with Tl(III) in acid solution is about 10^4 times faster than the rate of reaction with Fe(III), which suggests that in oxidation by Tl(III) part of the energy liberated in the second stage, $N_2H_3 \xrightarrow{-(e)} N_2H_2$ (almost certainly more exothermic than $N_2H_4 \xrightarrow{-(e)} N_2H_3$ since a π-bond is probably formed in N_2H_2), is able to lower the activation energy of reaction below that of the corresponding 1-electron-transfer process. This is only a way of saying that the successive 1-electron-transfer oxidations cannot be differentiated and that only one process can be distinguished in this and possibly other 2-electron-transfer oxidations of hydrazine. Because the stability expected for N_2H_2 is greater than that expected for N_2H_3, the oxidation of hydrazine appears to be a particularly favourable case for occurrence of a 2-electron-transfer reaction in a single step. That oxidation to N_2H_2 by V(V) is more rapid than that to N_2H_3 can now be understood even though the redox potential of $V(V)/V(III)$ (= 0·68) is appreciably smaller than that for $V(V)/V(IV)$ (= 1·00).

Though the suggestion that a 2-electron-transfer reaction may involve two successive 1-electron-transfer processes occurring before the reactants separate does not seem to be applicable to the oxidation of hydrazine, its application in other reactions is possible. For instance, Cahill and Taube (*ibid.*, p. 2312) concluded, on the basis of oxygen isotope fractionation in the reduction of hydrogen peroxide, that whereas Ti(III) is a 1-electron-transfer reagent, Fe(II), Cr(II), and Cu(I) behave as 2-electron-transfer reagents and are oxidised to Fe(IV), Cr(IV), and Cu(III) respectively. The annexed Table summarises measurements of the rates of reaction of several reducing agents with hydrogen peroxide, together with pertinent redox potentials. The temperature was 25°, and the hydrogen

	M(I)	Cr(II)	Sn(II)	Cu(I)	U(IV)	Fe(II)
	M(II)	Cr(III)	Sn(III)	Cu(II)	U(V)	Fe(III)
	M(III)	Cr(IV)	Sn(IV)	Cu(III)	U(VI)	Fe(IV)
Redox potentials	M(II)/M(I)	−0·41	>0·15 (<0·85)	0·15	0·62	0·77
	M(III)/M(II)	>1·5	<0·15	>1·8	0·05	>1·7
	M(III)/M(I)	>0·55	0·15	>0·97	0·33	>1·23
Acid, and concn.			HCl 2N	HCl 2·5N	H_2SO_4 0·67N	H_2SO_4 0·67N
Initial concn. of M(I)			0·020M	0·020M	0·020M	0·0328M
Half-life (sec.) (measured on [M(I)])		Short	<15	<15	≃15	<15

	M(I)	$PtCl_4^-$	Hg_2^{++}	Mn(II)	Tl(I)	Ag(I)
	M(II)	Pt(III)	Hg(I) + Hg(II)	Mn(III)	Tl(II)	Ag(II)
	M(III)	$PtCl_6^-$	2Hg(II)	Mn(IV)	Tl(III)	Ag(III)
Redox potentials	M(II)/M(I)	>0·68	>0·92	1·51	>1·25 (≃1·73)	1·98
	M(III)/M(II)	<0·68	<0·92	0·95	<1·25 (≃0·77)	≃2·0
	M(III)/M(I)	0·68	0·92	1·23	1·25	≃2·0
Acid, and concn.		HCl 0·67N	$HClO_4$ 0·67N	H_2SO_4 0·67N	H_2SO_4 0·67N	$HClO_4$ 0·67N
Initial concn. of M(I)		0·008M	0·067M	0·0772M	0·067M	0·067M
Half-life (measured on [M(I)])		≃3 hr.	N.R.	>150 hr.	N.R.	N.R.

N.R. = No reaction.

peroxide concentration was 0·040M. Although the validity of direct comparison between redox potentials and rates of reaction of electron-transfer reagents of different charge type with a common substrate is doubtful, a rough correlation is to be expected. It can be seen that the correlation between the half-life of reaction (measured on the concentration of metal ion) and the redox potential of the first 1-electron step is better than that between the half-life and the overall potential for the 2-electron step: compare for instance Cu(I) with Hg(I), and Fe(II) with Tl(I) or Mn(II). We suggest that, in this reaction, though Fe(IV), Cr(IV), and Cu(III) may be formed, reaction occurs in two stages, and it is only because a very strong oxidising agent, the hydroxyl radical, of redox potential ≃2·0, is produced adjacent to the Fe(III), Cr(III), or Cu(II) formed in the first, rate-determining stage of reaction that further oxidation giving the appearance of a 2-electron-transfer process can occur.

Experimental

Materials.—Commercial hydrogen peroxide (Laporte, stabiliser-free) was used. Fe(II) in usual sources of Ti(III) caused considerable decomposition of the peroxide, and our titanium trichloride solutions were prepared by electrolytic reduction of a pure specimen of tetrachloride in hydrochloric acid. Other reagents were of "AnalaR" grade or were purified by appropriate methods.

Oxidation of Hydrazine by the Hydroxyl Radical.—If hydrogen peroxide is titrated in acid solution with Ti(III) in the presence of hydrazine, the amount of Ti(III) consumed drops below the theoretical value [$2Ti(III) \equiv H_2O_2$]. However large the excess of hydrazine, the Ti(III) consumed never becomes less than half this theoretical amount. Neither Ti(III) nor hydrogen peroxide reacts with hydrazine under these conditions, nor does hydrogen peroxide in the presence of Ti(IV). These observations can be most simply explained if hydroxyl radicals, formed in the 1-electron-transfer reaction $Ti(III) + H_2O_2 \longrightarrow Ti(IV) + HO^- + OH$, may then

react with more Ti(III) [Ti(III) + OH ⟶ Ti(IV) + OH^-], or with $N_2H_5^+$, the proportion of these two reactions depending on the concentrations and the specific rate constants. We have used Ti(III), rather than other reducing agents, in this work since the oxidised form, Ti(IV), is unlikely to cause complications by acting as an oxidising agent.

The products of reaction were determined as follows. Hydrogen peroxide (0·1M) was dropped slowly from a burette into a closed vessel containing a stirred solution of titanous chloride (0·1M) and 0·014—0·182M-hydrazine hydrochloride. The acid strength (HCl) was *ca.* 0·5M and the total volume of solution 100 ml. When all the Ti(III) had been oxidised, the yellow colour of the Ti(IV)–H_2O_2 complex appeared and addition was stopped. Before the hydrogen peroxide titration the solution was degassed by freezing and pumping, and titration was performed at a pressure of *ca.* 50 mm. of pure nitrogen, a known volume being used so that the nitrogen evolved in the reaction could be found by a measurement of the total gas at the end of the reaction. When the end-point was reached, the contents of the titration vessel were frozen (liquid air), the gas in the vessel was pumped off (Töpler), and its pressure in a calibrated bulb measured. A small amount of oxygen ($1 - 3 \times 10^{-5}$ mole) in the evolved gas, formed by decomposition of the hydrogen peroxide, was estimated colorimetrically with alkaline pyrogallol and the amount of hydrogen peroxide consumed was corrected appropriately. Excess of hydrazine in the reaction mixture was estimated by iodine in alkaline solution, and then ammonia formed was found by the Kjeldahl method. Trial experiments showed that this procedure was suitable.

From the amounts of Ti(III) and hydrogen peroxide consumed, the number of hydroxyl radicals reacting with hydrazine was calculated. In the presence of small amounts of hydrazine, most of the hydroxyl radicals react with Ti(III) and the error in the hydroxyl stoicheiometry, OH/N_2H_4, became large. The values obtained agreed, within the limits of this error, with the hydroxyl stoicheiometry calculated from the amount of ammonia formed, on the assumption that the two limiting reactions for the oxidation of hydrazine in acid solution hold in this case. The nitrogen balance achieved was fairly good, as appears in the following Table of typical results.

Initial $[N_2H_4]$ (M)	$\Delta Ti(III)/\Delta H_2O_2$	OH/N_2H_4 stoicheiometry: from titration	OH/N_2H_4 stoicheiometry: from NH_3 formed	N_2H_4 decompd. (millimole)	N_2 formed (millimole)	NH_3 formed (millimole)	$2N_2 + NH_3 / 2\Delta N_2H_4$
0·182	1·50 ± 0·04	1·06 ± 0·1	1·07	2·995	1·52	2·93	1·00
0·047	1·66 ± 0·04	1·40 ± 0·2	1·39	1·415	0·79	1·23	0·99
0·024	1·75 ± 0·04	1·80 ± 0·3	1·66	0·769	0·50	0·60	1·04
0·014	1·84 ± 0·04	2·30 ± 0·6	1·96	0·368	0·25	0·25	1·02

We conclude from these experiments that the hydroxyl radical behaves in the same manner as the simple metal ions, in that both nitrogen and ammonia are products of its reaction. The stoicheiometry can be varied within wide limits; values in the region of 3 were obtained in other experiments.

Oxidation of Hydrazine in Acid Solution by Thallic Sulphate.—A stock thallic sulphate solution was prepared by Sherrill and Haas' method (*J. Amer. Chem. Soc.*, **1936**, **58**, 953) except that dithallium trioxide was precipitated by sodium hydroxide instead of by ammonia. The solution was standardised gravimetrically as thallous chromate, after reduction by sulphur dioxide, and also volumetrically by the Andrews' procedure (after similar reduction). Tl(I) in the solution was determined volumetrically in the same way. The volumetric method for Tl(III) described by Partington and Stonehill (*Trans. Faraday Soc.*, **1935**, **31**, 1357) gave values 1—2% low. The rate of reaction between Tl(III) and hydrazine in N-sulphuric acid was determined by removing samples of a mixture of equal amounts of 0·045M-Tl(III) and 0·1M-hydrazine, adding an excess of standard Ce(IV), and back-titrating the mixture with standard Fe(II) (ferroin indicator). Under these conditions Tl(I) is not oxidised by Ce(IV). Reaction between the latter and hydrazine is not stoicheiometric, but consistent results can be obtained if a standard procedure is used; we found that 1·06Ce(IV) ≡ N_2H_4. The reaction was complete within 2 min., and, approximately, 2Tl(III) ≡ N_2H_4. The stoicheiometry was determined accurately by estimating Tl(I), and, if present, excess of hydrazine, in similar mixtures by Andrews' method, 5 min. after mixing. It was necessary to know the time for complete reaction, since if 2Tl(III) ≏ N_2H_4, the titration would remain almost the same whether reaction was complete or not. The results were the same whichever reagent was in excess, and irrespective of the order of addition: (2·004 ± 0·005)Tl(III) ≡ N_2H_4. The residues were analysed for ammonia by Kjeldahl's method; within the limits of error (≡ ±0·2% of N_2H_4) no ammonia

was formed. At 80° traces (*ca.* 1%) of hydrazine were formed, as shown by distillation into a Fe(III) solution.

With the exception of Mn(III) the stoicheiometries of reaction of the substances listed in the first Table (p. 1381) were checked at room temperature, except where the method is already established as quantitative (iodate, bromate, and bromine). The methods used in previous work have been followed (for references see Audrieth and Ogg, *op. cit.*, p. 138).

Reactions with Hydrogen Peroxide.—The rates of reaction of 0·040M-hydrogen peroxide at 25° with various reagents under the conditions indicated in the second Table (p. 1384) were measured by quenching samples, at suitable times, in excess of standard Ce(IV) solution. The excess was determined by titration with a standard Fe(II) solution (ferroin as indicator). In most cases, as shown by trial experiments, this procedure caused oxidation of the unchanged reducing agent. Ag(I), Hg(I), and Tl(I) were unaffected; of the others, all except Mn were not reduced from their higher oxidation state in the subsequent back-titration against Fe(II). The hydrogen peroxide was oxidised by the Ce(IV) in all cases.

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283. *The Nitration of Guanidine in Sulphuric Acid. Part II.* Kinetics of N-Nitration of the Guanidinium Ion and Denitration of Nitroguanidine.*

By GWYN WILLIAMS and R. J. J. SIMKINS.

The conversion of guanidinium ion into nitroguanidine and the reverse denitration of nitroguanidine have measurable speeds in 71·5—83% sulphuric acid. In a given medium the rate of *N*-nitration is proportional to guanidinium ion and nitric acid concentrations, and it falls very sharply with increasing water content of the medium. Correlation of nitration speeds with the influence of medium upon the ionisation of triarylmethanol indicators suggests that the nitrating agent is the nitronium ion. In a given medium, the nitration velocity coefficient is reduced by increased initial concentration of guanidinium salt or of added inorganic salts. The reduction may be due largely to decreasing conversion of nitric acid into nitronium ion.

The rate of denitration of nitroguanidine is best represented as being proportional to nitroguanidine concentration; it falls with decreasing acidity of the medium, but less sharply than does the rate of nitration.

THE transformation of guanidine nitrate into nitroguanidine in sulphuric acid is reversible (Simkins and Williams, Part I, *loc. cit.*; Holstead and Lamberton, *J.*, 1952, 1886). The overall conversion into uncharged nitroguanidine (obtained by precipitating the product in water) is given by equation (1);† but the reaction in sulphuric acid should probably be represented by equation (2), in which the symbols G and P stand for the uncharged guanidine and nitroguanidine molecules, respectively.

$$^{+}H_2N{:}C(NH_2){\cdot}NO_3^{-} = HN{:}C(NH_2){\cdot}NH{\cdot}NO_2 + H_2O \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$GH^{+} + NO_2^{+} + HSO_4^{-} \rightleftharpoons PH^{+} + H_2SO_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Evidence is given below for the assumption that the nitronium ion is the nitrating agent.

In media containing more than 85% of sulphuric acid, the equilibrium between guanidine nitrate and nitroguanidine is established too quickly for the reaction rates to be measured (Part I, *loc. cit.*);‡ but, in the medium range 71·5—83% sulphuric acid, the

* Part I, *J.*, 1952, 3086.

† In neutral nitroguanidine the nitro-group is possibly attached to the imino-nitrogen atom (Barton, Hall, and Wright, *J. Amer. Chem. Soc.*, 1951, **73**, 2201); but, as pointed out in Part I, the distinction is unimportant for sulphuric acid solution, in which the compound is present as nitroguanidinium ion.

‡ With high concentrations of guanidine nitrate (*e.g.*, 1M), the slow dissolution of the starting material in the medium causes an apparently slow conversion; but the actual chemical reaction is fast.

approach to equilibrium, from either side, proceeds at a measurable rate. The choice of correct kinetic equations is assisted by the examination of the initial stages of the nitration and denitration processes, the reverse reaction then obtruding itself least.

N-Nitration of the Guanidinium Ion.—In order to vary the guanidine and nitric acid concentrations independently, guanidine carbonate has been used, as starting material, instead of guanidine nitrate; and the rate of approach from the left-hand side to equilibrium, in the reversible system (2), has been measured, in 71·5—83% sulphuric acid media, by dissolving guanidine carbonate in the given medium, mixing the solution with a solution of anhydrous nitric acid in the same medium, and following the fall of nitric acid concentration with time.

In these media, the empirical equilibrium products [K in Part I; cf. equation (5) below] lie well below the maximum value which they assume in about 88% sulphuric acid; but with the concentrations employed the equilibrium end-points generally correspond to 60—95% conversion of the initial reagent present in defect into nitroguanidine. Consequently, the initial stage of nitration may often be considered to be relatively little disturbed by the reverse reaction.

When $1/[HNO_3]$ (*e.g.*, in expt. 204) or log $\{[HNO_3]/[GH^+]\}$ (*e.g.*, in expts. 210, 211) (according to whether the initial reactant concentrations are equivalent or not) is plotted against time, the plot is initially linear, as shown in Figs. 1 and 2, whereas graphs of log $[HNO_3]$ against time are initially curved. This circumstance suggests that equation (3) is valid for the nitration process.

FIG. 1.

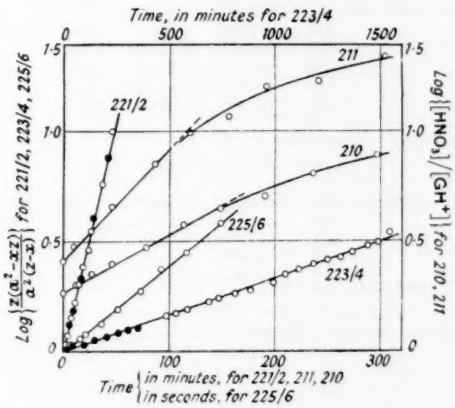
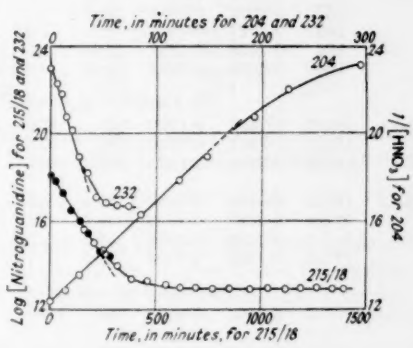


FIG. 2.



$$-d[HNO_3]/dt = k_2[HNO_3][GH^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Here, and elsewhere, $[HNO_3]$ denotes the analytically determined total concentration of nitric acid.

Influence of Initial Reagent Concentrations.—The results given in Table 1 (a) for velocity coefficients, k_2, derived graphically from equation (3) for the initial stages of nitration (cf. Fig. 2), show that k_2 changes little for a 13-fold variation of initial nitric acid concentration. The rate of *N*-nitration is thus nearly strictly proportional to nitric acid concentration, in accordance with equation (3).

On the other hand, the coefficient k_2, of equation (3), falls substantially with rising initial concentration of guanidinium ion [Table 1 (b)], though k_2 is not inversely proportional to initial $[GH^+]$. This result is not necessarily inconsistent with equation (3), because there is some evidence (see p. 1391) that variation of guanidinium salt concentration alters the acidity of the system to a sufficient extent to account for the variation of k_2 shown in Table 1 (b). When both reagent concentrations are varied in such a way that they are always equivalent, k_2 does not change greatly [Table 1 (c)].

Denitration of Nitroguanidine.—In experiments with nitroguanidine as starting material, not more than about 30% denitration occurs (in reasonable time; in the least acid media, equilibrium is approached very slowly). The initial stages of the denitration reactions (followed by measuring the rise of nitric acid concentration with time) therefore correspond to very small extents of conversion of nitroguanidine; and initial rates of denitration (to be as free as possible from the opposing nitration reaction) cannot be measured very accurately.

For the initial stage of each reaction the plot of log [nitroguanidine] against time is approximately linear (Fig. 2, expts. 232, 215/18), in accordance with equation (4):

$$-\mathrm{d}[\mathrm{PH}^+]/\mathrm{d}t = k_1[\mathrm{PH}^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

However, the reasonable range of validity of each plot in Fig. 2 extends over so small a conversion range that the linear graph is far from reliable as a test of equation (4). Nevertheless, when the initial concentration of nitroguanidine is increased 8-fold, in a given

TABLE 1.

Medium, % H_2SO_4	Expt. no.	Initial concn., M: Guanidine	HNO_3	$100k_2$, min.$^{-1}$	$100k_2'$	Medium, % H_2SO_4	Expt. no.	Initial concn., M: Guanidine	HNO_3	$100k_2$, min.$^{-1}$	$100k_2'$
(a) *Variation of initial nitric acid concentration at* 25°.											
75·47	206	0·2024	0·0509	3·56	—	—	208	0·2026	0·2446	3·73	—
	203	0·2025	0·0815	3·62	—		209	0·2019	0·2974	3·79	—
	202	0·2027	0·0996	3·55	3·62		210	0·2022	0·3744	3·59	—
	198	0·2020	0·1481	3·60	—		211	0·2019	0·5190	3·60	—
	190	0·2025	0·2037	3·60	4·10		212	0·2023	0·6649	3·91	—
(b) *Variation of initial guanidine concentration at* 25°.											
81·14	162/3	0·0957	0·1923	369	374		179/0	0·2951	0·1997	15·2	(15·6)
	160/1	0·1907	0·1930	209	259						
	164/5	0·3822	0·1923	158	161	75·47	194	0·0508	0·2028	6·52	6·91
							193	0·1013	0·2037	5·02	6·07
78·33	182/3	0·0494	0·1988	25·4	27·2		192	0·1525	0·2030	4·36	(4·84)
	177/8	0·0987	0·1990	23·0	24·1		190	0·2025	0·2037	3·60	4·10
	181	0·1486	0·1985	18·5	22·8		191	0·3034	0·2040	2·85	(3·66)
	175/6	0·1979	0·1985	18·9	(17·1)						
(c) *Equivalent reagent concentrations: variation of medium at* 25°.											
82·94	225/6	0·2004	0·2023	995	1100	75·47	205	0·0506	0·0509	4·15	—
							204	0·0813	0·0812	4·44	—
81·14	160/1	0·1907	0·1930	209	259		201	0·0993	0·0994	4·26	—
							200	0·1329	0·1331	4·07	—
79·24	221/2	0·2070	0·2093	73·0	64·8		199	0·1469	0·1480	4·00	—
							197	0·1752	0·1773	3·53	—
78·33	185	0·1040	0·1049	18·1	—		190	0·2025	0·2037	3·60	4·10
	186	0·1335	0·1345	19·9	—						
	175/6	0·1979	0·1985	18·9	17·1	71·48	223/4	0·2099	0·2081	0·254	(0·310)
	184	0·2349	0·2374	16·6	—						
(d) *Variation of temperature.*											
		Temp. 14·8°.						Temp. 35·0°.			
81·14	171	0·1908	0·1928	103	—	81·14	170	0·1914	0·1923	309	—
78·33	188	0·1972	0·1933	7·26	—	78·33	187	0·1974	0·1989	37·0	—
75·47	196	0·2033	0·2029	1·56	—	75·47	195	0·2025	0·2037	8·72	—

medium, the time taken for 5% denitration changes (and, in fact, *rises*) by not more than 50% (see col. 4, Table 2). Equation (4) seems, therefore, to be the best simple expression for the rate of denitration, with the reservation that k_1 (calculated from the linear graphs of Fig. 2) falls slowly with rising initial concentration of nitroguanidine in a given medium. In considering this "concentration variation" of k_1, it is to be recalled that the introduction of varying concentrations of the base nitroguanidine must alter the acidity of the system to different extents. As shown in Table 2, k_1 falls with decreasing acidity of the medium.

Equilibrium Constants.—A further illustration of the validity of the velocity coefficients, k_2 for nitration, and k_1 for denitration lies in comparing the values of the empirical

equilibrium product K of equation (5) (determined from *end-point measurements*, as described in Part I, the subscript e denoting equilibrium concentrations)

$$K = [PH^+]_e/[GH^+]_e[HNO_3]_e \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

with equilibrium products calculated from initial reaction rates by the relation $K = k_2/k_1$. The comparison is shown in Table 3. Agreement is reasonable in view of the experimental errors involved. The ratios k_2'/k_1' refer to coefficients derived from equation (6).

TABLE 2. *Denitration of nitroguanidine at* 25°.

Medium, % H_2SO_4	Expt. no.	Nitro-guanidine, initial concn., M	Time for 5% denitration, min.	10^4k_1
82·94	235/237/238	0·2084	—	277
79·24	232	0·0500	8·0	68·2
	231	0·1041	8·5	64·5
	230	0·1562	9·7	57·6
	228/229	0·2084	8·7	55·5
	233	0·3047	9·7	48·0
	234	0·4146	12·3	41·5
75·47	216/217	0·1000	50	10·6
	207/213/214	0·2024	57	9·45
	215/218	0·4000	77	6·80
71·48	239/240	0·2082	—	1·80

TABLE 3. *Equilibrium products for* 0·2M-*initial reagent concentrations.*

Medium, % H_2SO_4	82·94	79·24	75·47	71·48
K (end-point)	294	114	44·6	—
k_2/k_1	359	132	38·1	14·1
k_2'/k_1'	332	146	47·1	14·7

The Reversible Kinetic Equation for a Given Medium.—Combination of equations (3) and (4) gives equation (6) as an expression of the reaction rate in the reversible process, in a given medium :

$$-d[HNO_3]/dt = k_2[GH^+][HNO_3] - k_1[PH^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

If a and b are the initial concentrations of guanidinium ion and nitric acid respectively; and if x and z are the concentrations of nitroguanidine at time t and at equilibrium, respectively, integration of (6) gives (7) or (8), according to whether a equals b, or not.

$$k_2t = \frac{2{\cdot}303z}{a^2 - z^2} \log\left\{\frac{z}{a^2} \cdot \frac{a^2 - xz}{z - x}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

$$k_2t = \frac{2{\cdot}303z}{ab - z^2} \log\left\{\frac{z}{ab} \cdot \frac{ab - xz}{z - x}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Experimentally (as illustrated in Fig. 1, expts. 221/2, 223/4, 225/6), the log terms in (7) and (8) are found to be linear with time for those experiments in Table 1 which were pursued far enough to give z. N-Nitration velocity coefficients, calculated from the linear graphs of (7) and (8), are shown as k_2' in Table 1. As a rule, they do not differ greatly from the values of k_2, calculated, by equation (3), from the measurements of initial rates. Figures for k_2' in parentheses are based on extrapolated values of z.

The Rate-determining Step in N-*Nitration.*—Velocities of N-nitration of the guanidinium ion in 76—82% sulphuric acid are close enough (differing at most by a factor of 2 in a given medium) to the rates of nuclear nitration of the trimethyl-*p*-tolylammonium ion (Williams and Lowen, *J.*, 1950, 3312; Lowen, Murray, and Williams, *ibid.*, p. 3318) in the same media, to raise the suspicion that the measured rate might be the rate of conversion of nitric acid into the actual nitrating agent, as happens in other media (Hughes, Ingold, and Reed, *J.*, 1950, 2400). The possibility is excluded because, in the same medium range, toluene-*p*-sulphonic acid is nitrated much more rapidly than either compound. Thus, 0·085M-toluene-*p*-sulphonic acid was completely mononitrated in less than 1·5 min. in 79% sulphuric acid at 25°, whereas 0·2M-guanidine required 51 min. for 81% nitration (equilibrium) in the same medium. The guanidinium ion is not, therefore, being rapidly attacked by a slowly formed nitrating agent.

The Nitrating Agent in N-*Nitration.*—The velocity coefficient, k_2 of equation (3), for *N*-nitration of the guanidinium ion falls by a factor of 4×10^3 in the medium range 83—71·5% sulphuric acid [Table 1 (c)]; and therefore decreases far more steeply than the vapour pressure of nitric acid over its solutions in the same media. The argument against supposing the un-ionised nitric acid molecule to be the nitrating agent is the same as for the nuclear nitration of the trimethyl-*p*-tolylammonium ion (*loc. cit.*). A positive test for nitration by the nitronium ion can also be applied to guanidine, as to the aromatic ion (*loc. cit.*, cf. Westheimer and Kharasch, *J. Amer. Chem. Soc.*, 1946, **68**, 1871).

If the experimental and theoretical rates of *N*-nitration are given by equations (3) and (9), respectively, and if equation (10) defines an acidity function J_0, governing the ionisation of a carbinol ROH (Lowen, Murray, and Williams, *loc. cit.*; Gold and Hawes, *J.*, 1951, 2102), then, provided that (11) holds, with b independent of medium, and that (12) is valid throughout the medium range, equation (13) follows (Bonner, Bowyer, and

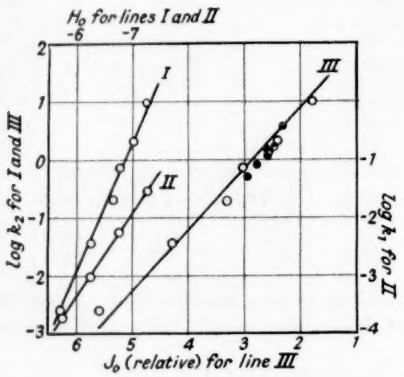


FIG. 3.

⊗ *Varying guanidine concentration.*
◓ *With added* $KHSO_4$.
● *With added* $(NH_4)_2SO_4$.

Williams, *J.*, 1952, 3274), by analogy with an argument due to Hammett and Paul (*J. Amer. Chem. Soc.*, 1934, **56**, 830).

$$-d[HNO_3]/dt = k_2^{\circ}[NO_2^+][GH^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

$$J_0 = -pK_{NO_2\cdot OH} - \log([NO_2^+]/[NO_2\cdot OH]) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

$$[NO_2^+]/[NO_2\cdot OH] = b \,.\, [R^+]/[R\cdot OH] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

$$[HNO_3] = [NO_2^+] + [NO_2\cdot OH] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

$$\log k_2 = \log k_2^{\circ} - pK_{NO_2\cdot OH} - J_0 - \log\left\{1 + \frac{[NO_2^+]}{[NO_2\cdot OH]}\right\} \quad . \quad . \quad . \quad . \quad . \quad (13)$$

In 83—71% sulphuric acid media, $[NO_2\cdot OH] \gg [NO_2^+]$ (cf. Bonner and Williams, *Chem. and Ind.*, 1951, 820). Consequently, from (14), the variation of log k_2 with medium

$$\log k_2 = \log k_2^{\circ} - pK_{NO_2\cdot OH} - J_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

composition should be connected with that of J_0 ($K_{NO_2\cdot OH}$ having been defined as a thermodynamic equilibrium constant) by a straight line of negative unit gradient, except in so far as k_2° varies with medium.

The acidity function J_0 is given in absolute terms by the alternative definition, $J_0 = H_0 + \log a_{H_2O}$ (Gold and Hawes, *loc. cit.*); but, when calculated from this equation, J_0 carries the combined errors in the measurements of both H_0 (Hammett's acidity function) and a_{H_2O}. We have therefore used relative values of J_0 derived directly from measurements of the extent of ionisation of carbinol indicators (Murray and Williams, *J.*, 1950, 3322).

Log k_2 is plotted against J_0 (rel.) in Fig. 3 (line III). The points are somewhat scattered, but the slope, calculated by the method of least squares, for the line shown in the diagram,

is −1·06 in accordance with equation (14).* If the $H_2NO_3^+$ ion were the nitrating agent, log k_2 should give a straight line of unit slope when plotted against $-H_0$. Fig. 3 also shows that the graph of log k_2 against H_0 has a slope of −2·2 (line I).

The graphs in Fig. 3 suffice to show clearly that the hypothesis of *N*-nitration by the NO_2^+ ion is preferable to that of nitration by the $H_2NO_3^+$ ion (cf. Blackall and Hughes, *Nature*, 1952, **170**, 972). Evidently, however, the conformation of the points to the calculated line

$$\log k_2 = -1{\cdot}056J_0 + 3{\cdot}008 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

is not exact. A curve could be drawn through them. The curvature (if real) could be due (*a*) to experimental error, (*b*) to a medium variation of *b* in equation (11), (*c*) to a medium variation of k_2° in equation (14). Insufficient information is available at present to warrant a decision between these possibilities.

It is also difficult to judge whether appreciable ionisation of nitric acid to nitrate ion impairs the validity of equation (12) in the most aqueous media employed (*e.g.*, in 71·5% sulphuric acid). Raman spectra of nitric acid are not decisive in such solvents (Chédin, *Ann. Chim.*, 1937, **8**, 243); but the ultra-violet absorption maximum of the nitrate ion is not evident in solutions of nitric acid in 70% sulphuric acid (unpublished experiments; cf. Schaefer, *Z. anorg. Chem.*, 1916, **98**, 77). Evidence for hydrated forms of molecular nitric acid in nitric acid–water mixtures has recently been discussed by Chédin (*J. Chim. phys.*, 1952, **49**, 109).

Influence of Initial Guanidine Concentration.—The variation of k_2 with initial guanidine concentration in a given medium, shown in Table 1(b), may be due (*a*) to an influence of changing concentration upon the theoretical velocity coefficient k_2° of equation (9), (*b*) to an influence of the guanidine salt upon the acidity of the medium with a consequent alteration of the degree of ionisation of nitric acid to the nitronium ion, or (*c*) to both.

Influence of Added Salts.—The effect referred to in the preceding paragraph is closely connected with the influence of added inorganic salts upon the rate of *N*-nitration shown by the results in Table 4. The influence of salts may also be considered under the headings (*a*), (*b*), and (*c*) of the preceding section. There is provisional evidence that (*b*) is an important factor.

TABLE 4. *Influence of added salts at 25°.*

Medium, 81·14% H_2SO_4. Initial reagent concentrations, 0·2M.

Expt. no.	Added salt and concn., M.		$100k_2$	Expt. no.	Added salt and concn., M.		$100k_2$
160/161	—	—	209	172	$(NH_4)_2SO_4$	0·285	114
				173	$(NH_4)_2SO_4$	0·599	78·7
168	$KHSO_4$	0·299	163	174	$(NH_4)_2SO_4$	0·861	47·5
169	$KHSO_4$	0·557	154				

Variation of the Extent of Ionisation of Nitric Acid.—It is an empirical fact that additions of salts (including guanidine salts) bring about an apparent change in the extent of ionisation of a triarylcarbinol indicator in media within the range 71·5—83% sulphuric acid as measured colorimetrically (at a single wave-length) with a photoelectric absorptiometer. If the alteration of intensity of light absorption is really due to altered extent of ionisation, then J_0 for the medium—equation (10)—is affected by salt additions; and these will also influence the extent of ionisation of nitric acid to nitronium ion. Unpublished experiments (by Dr. M. A. Murray) give ΔJ_0/mole for potassium hydrogen sulphate, ammonium sulphate, and guanidine carbonate as −0·2, −0·6, and −2·0, respectively, for media in the region of 80% sulphuric acid. The negative sign here indicates lowering of acidity. These figures are approximate and provisional. If they are used to calculate changes of J_0 brought about by the salt concentrations shown in Table 1(b) and in Table 4, and if these concentrations influence nitration speed mainly by their effects upon nitronium-ion concentration, then the corresponding changes of nitration speed should be accommodated by equation (14). Correlation of log k_2 with the calculated values of J_0 is shown in Fig. 3.

* The less extensive results at other temperatures—Table 1 (d)—give approximately parallel lines. If log k_2 is plotted against Gold and Hawes's values for J_0, the line has a slightly steeper slope than that shown in Fig. 3.

The calculated salt effects appear to be of the right order of magnitude, but the conclusions must be accepted with reserve, pending completion of absorption experiments on carbinol indicators over a range of wave-lengths.

Effect of Temperature upon N-*Nitration.*—Results at different temperatures are shown in Table 1 (d). The Arrhenius equations for 78·3 and 74·5% sulphuric acid are, respectively, $k_2 = 1{\cdot}60 \times 10^7$ exp. $(-13{,}230/\boldsymbol{RT})$ and $k_2 = 7{\cdot}71 \times 10^7$ exp. $(-13{,}790/\boldsymbol{RT})$ l. mole^{-1} sec.$^{-1}$. The results for 81·1% sulphuric acid are discordant and require confirmation. They give $k_2 = 8{\cdot}15 \times 10^5$ exp. $(-8{,}940/\boldsymbol{RT})$.

Nitration and Denitration.—Wright and his colleagues have shown (*Canad. J. Res.*, 1948, **26**, *B*, 104, 114, 257) that easy *N*-nitration to form nitramines is associated with weak basicity of the nitrogen atom at which reaction takes place. Their hypothesis of preliminary formation of an amine–nitric acid complex has been interpreted by Lamberton (*Quart. Reviews*, 1951, **5**, 75) in terms of action by the nitronium ion. The guanidinium ion is a very weak base (unpublished experiments) and its ready *N*-nitration is consistent with these views. The present work supports the hypothesis of nitration by the nitronium ion in 83—71·5% sulphuric acid. A possible scheme for the process (Lamberton, *loc. cit.*) is :

$$NO_2^+ + H_2\overset{+}{N}{:}C(NH_2)_2 \rightleftharpoons H_2\overset{+}{N}{:}C(NH_2)\cdot\overset{+}{N}H_2\cdot NO_2 \rightleftharpoons H_2\overset{+}{N}{:}C(NH_2)\cdot NH\cdot NO_2 + H^+ . \quad (16)$$

The coefficient k_1 for the denitration of nitroguanidine falls by a factor of 150 over the range 83—71·5% sulphuric acid (Table 2). If the rate-determining step in the denitration of nitroguanidine were the extrusion of nitronium ion from the transition complex of (16), produced from nitroguanidinium ion by rapid proton uptake, then by Hammett and Paul's argument (*loc. cit.*) log k_1 might be connected by a line of unit negative gradient with the acidity function H_+ governing proton uptake by a positively charged base. No values are available for H_+ in sulphuric acid. The graph of log k_1 against H_0 is shown in Fig. 3 (line II). It has gradient −1·4. The results are too few to warrant any firm conclusions about the mechanism of denitration.

Experimental

Materials.—" AnalaR " guanidine carbonate was purified by precipitation from a solution in boiling water by addition of alcohol, and dried (P_2O_5) at 50°/10 mm. for 48 hours (Found, for two samples: C, 20·5, 19·8; H, 6·55, 6·2; N, 46·6, 47·0. Calc. for $C_3H_{12}O_3N_6$: C, 20·0; H, 6·7; N, 46·7%).

Inorganic salts were " AnalaR " materials dried before use. All other materials were prepared and purified as described in Part I (*loc. cit.*).

Velocity Measurements.—The guanidine solution was prepared by dissolving guanidine carbonate in sulphuric acid–water medium in a 50-ml. flask in an ice–water bath. After being made up to volume at thermostat temperature, the solution was transferred to a three-necked reaction vessel. To it (with stirring) was added a solution of nitric acid in the same medium. Timing of the reaction was started when the addition of the nitric acid solution (generally requiring 30 sec.) was one-half completed. Corrections were applied for drainage residues left in the standard flasks in which the two reagent solutions had been prepared. Samples for analysis were withdrawn in a 5-ml. pipette fitted with a stopcock. These were poured into 55 ml. of water at recorded times.

For certain very rapid reactions, 5-ml. samples of nitric acid solution were added from B.19 cone caps of 5-ml. capacity to 5-ml. samples of guanidine solution in 10-ml. containers fitted with B.19 sockets, with vigorous shaking. For sampling, the whole contents of each 10-ml. vessel were poured into 10 ml. of water. With this method a sample could be withdrawn within 6 seconds after mixing of the reagents. With a series of the 10-ml. reaction vessels, samples could be timed at 3-second intervals if required (cf. expt. 225/6 in Fig. 1).

The samples extracted from the reaction mixture at recorded times were analysed for nitric acid, after destruction of nitroguanidine, by the method described in Part I (*loc. cit.*).

Duplicate experiments (see Tables), with independent reaction mixtures, were commonly combined to give one reaction curve. Reproducibility may be judged from examples given in Figs. 1 and 2.

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284. 2 : 5-*Dihydroxy*-3 : 6-*dimethoxyacetophenone and Its Degradation by Bromine.*

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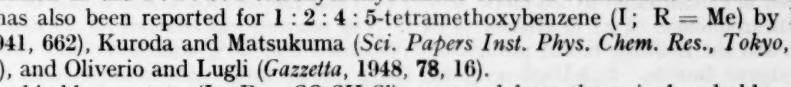
Attempts to introduce a chloroacetyl or a formyl group into 2 : 5-dimethoxyquinol and its ethers have failed. 2 : 5-Dihydroxy-3 : 6-dimethoxyacetophenone has been obtained, but bromination has resulted in degradation to bromanilic acid (V; R = H).

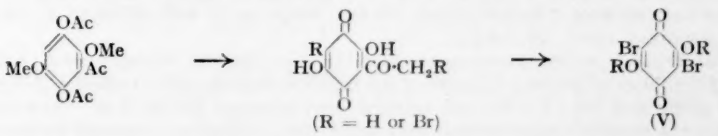
For synthesis of a furanochromone isomeric with kellin, 5-hydroxy-4 : 7-dimethoxycoumaran was required. This necessitated the introduction of either a chloroacetyl or a formyl substituent into 2 : 5-dimethoxyquinol (I; R = H), which was obtained by reduction of 2 : 5-dimethoxybenzoquinone with stannous chloride in acid solution (cf. Nietzki and Rechberg, *Ber.*, 1890, **23**, 1211). The quinol, however, did not undergo the Friedel–Crafts, Reimer–Tiemann, Hoesch, or Gattermann reaction. The more readily soluble diethoxyquinol, prepared by ethylation of 2 : 5-dihydroxybenzoquinone and reduction of the resulting 2 : 5-diethoxybenzoquinone as above, also resisted substitution. The dibenzyl ether (I; R = CH_2Ph) and the dicarbethoxy-derivative (I; R = CO_2Et) showed the same resistance in the Hoesch and the Gattermann reaction. This inertness to nuclear substitution in the 1 : 2 : 4 : 5-tetrahydroxybenzene series is remarkable: similar resistance has also been reported for 1 : 2 : 4 : 5-tetramethoxybenzene (I; R = Me) by Baker (*J.*, 1941, 662), Kuroda and Matsukuma (*Sci. Papers Inst. Phys. Chem. Res., Tokyo*, 1932, **18**, 51), and Oliverio and Lugli (*Gazzetta*, 1948, **78**, 16).

The bischloroacetate (I; R = $CO{\cdot}CH_2Cl$), prepared from the quinol and chloroacetic anhydride, failed to rearrange to an identifiable product when treated with aluminium chloride or boron trifluoride. The diacetate (I; R = Ac) gave only amorphous material when treated with aluminium chloride, but when heated with the boron trifluoride–ether complex in acetic acid smoothly rearranged to yield 2 : 5-dihydroxy-3 : 6-dimethoxyacetophenone (II; R = H) in satisfactory yield. Aqueous solutions of this ketone were readily oxidised by air to a dark red solid believed to be 3-acetyl-2 : 5-dimethoxybenzoquinone.



No derivative of 2 : 3 : 5 : 6-tetrahydroxyacetophenone has previously been synthesised, although 2 : 3 : 5 : 6-tetrahydroxy-ω-methoxyacetophenone (III) has been reported as a degradation product of the naturally occurring gardenin by Bose and Nath (*J. Indian Chem. Soc.*, 1938, **15**, 139).

Since the introduction of a chloroacetyl or a formyl group proved impossible, the quinol (II; R = H) was brominated in an attempt to prepare the phenacyl bromide (IV). The quinol or its acetate with bromine in acetic acid gave, however, bromanilic acid (V; R = H) identified by its properties and analysis and by comparison of the di-



acetates (Graebe and Weltner, *Annalen*, 1891, **263**, 31; Jackson and Bolton, *J. Amer. Chem. Soc.*, 1914, **36**, 1473). The yield was influenced by the amount of bromine used, being a maximum with excess. This reaction can be explained as follows. The hydrogen bromide formed during an initial bromination step hydrolyses the acetoxy-groups, and the resultant

quinol is oxidised to a 2 : 5-dimethoxybenzoquinone derivative in which the methoxyl groups are particularly subject to acid hydrolysis. The acetyl group in the ensuing acetylbenzoquinone derivative is incorporated in a β-diketone system and hence is easily replaced by bromine. Bromination in the initially vacant nuclear position yields bromanilic acid. Since the complications owe their origin to the hydrogen bromide produced in the reaction, bromination was next attempted in chloroform in the presence of calcium carbonate; but no reaction then occurred, even under irradiation with ultra-violet light.

Experimental

2 : 5-*Dimethoxyquinol* (I; R = H) (cf. Nietzki and Rechberg, *loc. cit.*).—Crude 2 : 5-dimethoxybenzoquinone (15 g.) (Knoevenagel and Bückel, *Ber.*, 1901, **34**, 3993) was added to a solution of stannous chloride (25 g.) in concentrated hydrochloric acid (25 c.c.), and the resulting pasty mass refluxed until a clear solution was obtained (*ca.* 15 min.). On cooling, a mass of dark needles appeared which, on recrystallisation from water containing sulphur dioxide, yielded 2 : 5-dimethoxyquinol (9 g., 60%) as colourless needles, m. p. 166°.

2 : 5-*Diethoxybenzoquinone*.—2 : 5-Dihydroxybenzoquinone (Jones and Shonle, *J. Amer. Chem. Soc.*, 1945, **67**, 1034) was dissolved in ethanolic hydrogen chloride (50 c.c.) under reflux (30 min.). Cooling the brown solution yielded 2 : 5-diethoxybenzoquinone as brown crystals which were filtered off (3 g., 50%) and formed yellow leaflets, m. p. 183°, on recrystallisation from ethanol.

2 : 5-*Diethoxyquinol* (cf. Nietzki and Rechberg, *loc. cit.*).—Stannous chloride (2·5 g.) was dissolved in concentrated hydrochloric acid (5 c.c.) and the solution added to one of 2 : 5-diethoxybenzoquinone (2 g.) in ethanol (5 c.c.). The mixture was refluxed for 20 min., then cooled, and the resulting brown precipitate crystallised from 30% aqueous ethanol saturated with sulphur dioxide. 2 : 5-Diethoxyquinol (1·1 g., 55%) formed colourless needles, rapidly becoming pink in air, m. p. 138°.

2 : 5-*Biscarbethoxyoxy*-1 : 4-*dimethoxybenzene* (I; R = CO_2Et).—2 : 5-Dimethoxyquinol (7·5 g.), anhydrous potassium carbonate (15 g.), ethyl chloroformate (12 c.c.), and anhydrous acetone (100 c.c.) were refluxed for 6 hr. with stirring, then diluted with further acetone (100 c.c.) and filtered hot. Evaporation left a solid which on crystallisation from ethanol yielded 2 : 5-*biscarbethoxyoxy*-1 : 4-*dimethoxybenzene* (8·5 g., 66%) as needles, m. p. 162° (Found: C, 53·9; H, 5·8. $C_{14}H_{18}O_8$ requires C, 53·5; H, 5·8%).

1 : 4-*Dibenzyloxy*-2 : 5-*dimethoxybenzene* (I; R = CH_2Ph).—2 : 5-Dimethoxyquinol (10 g.), acetone (150 c.c.), anhydrous potassium carbonate (11·8 g.), and anhydrous potassium iodide (17·6 g.) were refluxed with stirring. Benzyl chloride (13 c.c.) was added and stirring and refluxing were continued for 20 hr. The hot acetone solution was filtered and the residue washed with hot acetone (100 c.c.), the combined filtrate and washings then being evaporated to 50 c.c. On cooling, crystals appeared which on recrystallisation from acetone yielded 1 : 4-*dibenzyloxy*-2 : 5-*dimethoxybenzene* (12·7 g., 62%) as plates, m. p. 145° (Found: C, 75·4; H, 6·3. $C_{22}H_{22}O_4$ requires C, 75·4; H, 6·3%).

1 : 4-*Bischloroacetoxy*-2 : 5-*dimethoxybenzene* (I; R = $CO{\cdot}CH_2Cl$).—2 : 5-Dimethoxyquinol (5 g.) was heated on a water-bath with chloroacetic anhydride (Diels and Okada, *Ber.*, 1911, **44**, 3333) (25 g.) for 1 hr. The solution was then allowed to cool and solidify. Ether (100 c.c.) was added and the insoluble ester filtered off. Crystallisation from chloroform yielded 1 : 4-*bischloroacetoxy*-2 : 5-*dimethoxybenzene* (7·5 g., 40%) as plates, m. p. 190° (Found: C, 44·5; H, 3·9. $C_{12}H_{12}O_6Cl_2$ requires C, 44·6; H, 3·7%).

1 : 4-*Diacetoxy*-2 : 5-*dimethoxybenzene* (I; R = Ac).—2 : 5-Dimethoxyquinol (10 g.) was refluxed in acetic anhydride (40 c.c.) for 1 hr. After cooling, the *diacetate* was collected; crystallised from ethanol it formed plates (13·5 g., 90%), m. p. 185° (Found: C, 56·8; H, 5·8. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·6%).

2 : 5-*Dihydroxy*-3 : 6-*dimethoxyacetophenone* (II; R = H).—1 : 4-Diacetoxy-2 : 5-dimethoxybenzene (2·5 g.) was added to a mixture of the boron trifluoride–ether complex (1·5 g.; 48% of BF_3) and acetic acid (10 c.c.), and the mixture kept at about 75° for 2 hr. The mixture was then cooled, the resulting paste treated with water (12 c.c.) and concentrated hydrochloric acid (3 c.c.), and the mixture refluxed until a clear solution was obtained. On cooling, needles appeared; recrystallisation from water containing sulphur dioxide gave 2 : 5-*dihydroxy*-3 : 6-*dimethoxyacetophenone* (1 g., 55%), m. p. 170° (Found: C, 56·3; H, 5·8. $C_{10}H_{12}O_5$ requires C, 56·6; H, 5·7%). Aqueous solutions of this compound deposited, on exposure to air, red needles, m. p. 301° (decomp.), presumably 3-acetyl-2 : 5-dimethoxybenzoquinone.

The ketone (0·5 g.) was shaken in aqueous sodium hydroxide (10 c.c.; 35%) with methyl sulphate (2·5 c.c.). The resulting **2 : 3 : 5 : 6-*tetramethoxyacetophenone*** (0·4 g., 70%) formed needles, m. p. 101°, from water (Found : C, 60·1; H, 6·9. $C_{12}H_{16}O_5$ requires C, 60·0; H, 6·7%).

The *diacetate*, prepared by means of hot acetic anhydride (8 c.c.; 1 hr.), formed cubes (95%), m. p. 190°, from ethanol (Found : C, 56·6; H, 5·4. $C_{14}H_{16}O_7$ requires C, 56·8; H, 5·4%).

Bromanilic Acid (V; R = H).—(*a*) **2 : 5-Dihydroxy-3 : 6-dimethoxyacetophenone** (0·5 g.) in acetic acid (8 c.c.) was treated with bromine (0·6 g.) in acetic acid (2 c.c.). The mixture was heated on a steam-bath for 1 hr., then allowed to cool. A yellow solid appeared which was removed and crystallised from acetic acid. Bromanilic acid formed yellow needles drying to a red powder (0·55 g., 75%), subliming at 280—290° (Found : C, 24·9; H, 0·9. Calc. for $C_6H_2O_4Br_2$: C, 24·2; H, 0·7%).

(*b*) Repetition of this experiment but with **1 : 4-diacetoxy-2 : 5-dimethoxyacetophenone** (0·5 g.) yielded bromanilic acid (0·35 g., 69%).

2 : 5-Diacetoxy-3 : 6-dibromobenzoquinone (V; R = Ac), prepared by Jackson and Bolton's method (*loc. cit.*) using bromanilic acid obtained both as above and by Graebe and Weltner's method, had m. p. 204°, admixture producing no depression.

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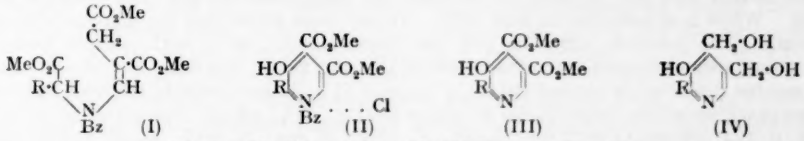
HUDDERSFIELD TECHNICAL COLLEGE. [*Received, January 26th,* 1953.]

285. *Synthesis of Analogues of Pyridoxine.*

By MRS. H. DAVOLL and F. B. KIPPING.

Three analogues of pyridoxine, the 2-*iso*propyl, 2-*iso*butyl, and 2-phenyl derivatives of 3-hydroxy-4 : 5-bishydroxymethylpyridine, have been synthesised. They have little or no pyridoxine-like activity.

COHEN, HAWORTH, and HUGHES (*J.*, 1952, 4374) have described a synthesis of pyridoxine, and Cohen and Silk (*ibid.*, p. 4386) have applied this to an analogue of pyridoxine with a benzyl instead of the methyl group in the 2-position. Syntheses by the same methods of three more analogues of pyridoxine with respectively an *iso*propyl, an *iso*butyl, and a phenyl group in this position are now described : the work was indeed suggested to us by Professor F. Bergel in order to study the pyridoxine activity of such compounds. The results of the biological tests carried out by Roche Products Ltd. showed no pyridoxine activity, except for the *iso*propyl analogue, when tested in the presence of pyridoxine : in this case a pyridoxine activity 400 times less than that of pyridoxine was found. These results are similar to those of Cohen and Silk (*loc. cit.*) for the benzyl analogue.



(*a*) R = Me_2CH; (*b*) R = $Me_2CH{\cdot}CH_2$; (*c*) R = Ph.

The methyl ester of an α-benzylamino-acid was condensed with methyl α-formylsuccinate to give a compound of type (I) which was cyclised with sodium or sodium ethoxide and treated with sulphuryl chloride; the resulting pyridinium salt (II) was then debenzylated by reduction to (III). In the case of the phenyl analogue, (III*c*) was converted into (IV*c*) both by the method of Cohen, Haworth, and Hughes (*loc. cit.*) and by the subsequently discovered reduction with lithium aluminium hydride (cf. also Jones and Kornfeld, *J. Amer. Chem. Soc.*, 1951, **73**, 107) : with (III*a*) and (III*b*) only the latter method was used.

Experimental

Methyl α-Benzylaminoisovalerate.—(*a*) Valine methyl ester [3·57 g.; b. p. 58—58·5°/12 mm.; prepared from the acid (*Org. Synth.*, **20**, 106) by the Fischer–Speier method] and benzaldehyde (3·16 g.) were stirred in methanol (25 ml.) with a little charcoal during 2 hr. The solution was filtered and hydrogenated at atmospheric pressure (10% palladised charcoal; 30 mg.); after filtration and removal of the solvent at 40°, distillation gave *methyl α-benzylaminoisovalerate* (5·15 g., 86%; b. p. 84·5°/0·3 mm.) as a colourless oil (Found: C, 70·6; H, 9·2; N, 6·7. $C_{13}H_{19}O_2N$ requires C, 70·6; H, 8·6; N, 6·3%). In ether this gave the *hydrochloride* which crystallised from ethanol–ether in needles, m. p. 181° (Found: C, 60·8; H, 7·5; N, 6·0. $C_{13}H_{20}O_2NCl$ requires C, 60·6; H, 7·8; N, 5·4%).

(*b*) α-Bromoisovaleric acid (18·1 g.) was methylated with diazomethane in ether to give methyl α-bromoisovalerate, b. p. 170—175° (15·5 g., 80%). This ester (15·5 g.) was heated with benzylamine (17 g.) at 120° during 4 hr., water added to the cooled mixture, and the product extracted with ether, dried (Na_2SO_4), and distilled (6·9 g., 39%: b. p. 100°/0·5 mm.).

Dimethyl N-Benzyl-N-(1-carbomethoxyisobutyl)aminomethylenesuccinate (I*a*).—Methyl α-benzylaminoisovalerate (6·9 g.) and dimethyl formylsuccinate (6 g.) were heated together during 1 hr. at 100°, and then under about 15 mm. during ½ hr. Distillation of the residue gave the *ester* (I*a*) (9·8 g., 83%; b. p. 175°/5 × 10^{-4} mm.) as a viscous yellow oil (Found: C, 64·0; H, 7·4; N, 3·8. $C_{20}H_{27}O_6N$ requires C, 63·6; H, 7·2; N, 3·7%).

1-Benzyl-4 : 5-dicarbomethoxy-3-hydroxy-2-isopropylpyridinium Chloride (II*a*).—The above ester (7·9 g.) in pure dry benzene (100 ml.) was added to powdered sodium (0·49 g.), and the mixture refluxed in nitrogen during 6 hr. A mixture of water (6·7 ml.), ice (3 g.), acetic acid (1·21 ml.), and 2N-sulphuric acid (0·35 ml.) was added to the cooled product, and the benzene layer washed successively with water and aqueous sodium hydrogen carbonate and dried (Na_2SO_4). Drying was completed by evaporation of some of the benzene, sulphuryl chloride (1·44 ml.) added dropwise at 40°, and the mixture kept at room temperature during 2 hr. The benzene was decanted from the oil which had separated and the latter warmed at 40° under reduced pressure (water-pump) during 2 hr. The resulting frothy product crystallised when warmed with acetone (5 ml.), and was washed with the same solvent till colourless [m. p. 143° (decomp.); 4·93 g., 62%]. Crystallisation from ethanol–ether gave prisms of the *pyridinium chloride*, m. p. 146° (decomp.) (3·77 g.) (Found: C, 58·5; H, 6·1; N, 3·6. $C_{19}H_{22}O_5NCl,\frac{1}{2}H_2O$ requires C, 58·7; H, 5·9; N, 3·6%).

Dimethyl 3-Hydroxy-2-isopropylpyridine-4 : 5-dicarboxylate (III*a*).—The above pyridinium chloride (1·75 g.) in methanol was reduced with hydrogen (0·1 g. of 10% palladised charcoal); the absorption was quantitative. The product was filtered, methanol and toluene were removed under reduced pressure, and the crystalline residue was dissolved in water (5 ml.) and methanol (2 ml.). Addition of sodium acetate trihydrate (1·24 g.) in water (3 ml.) to the ice-cold solution gave an oil which crystallised (1·04 g., 90%). Crystallisation from aqueous ethanol gave the *ester*, prisms, m. p. 68° (0·67 g.) (Found: C, 57·2; H, 6·1; N, 5·5. $C_{12}H_{15}O_5N$ requires C, 56·9; H, 5·9; N, 5·5%).

3-Hydroxy-4 : 5-bishydroxymethyl-2-isopropylpyridine (IV*a*).—The ester (III*a*) (0·835 g.) was placed in a Soxhlet thimble over lithium aluminium hydride (0·3 g.) in ether (50 ml.), and the solution heated with stirring until all the ester had been dissolved and then during a further 20 min. Water and hydrochloric acid (10%; 10 ml.) were added and the mixture was shaken (10 min.). The solution, after its pH had been brought to 7 with sodium hydroxide, was continuously extracted with ether (100 ml.) during 28 hr., the ether evaporated, and the dried residue dissolved in alcohol (10 ml.); passage of hydrogen chloride followed by addition of ether precipitated the *hydrochloride* as prisms (0·41 g., 58%) which, crystallised from acetone, had m. p. 192° (decomp.) (0·37 g.) (Found: C, 51·4; H, 6·6; N, 6·45. $C_{10}H_{16}O_3NCl$ requires C, 51·4; H, 6·9; N, 6·0%). In a second experiment the *base* (IV*a*) was obtained by subliming the residue from the evaporation of the ether at 160°/10^{-4} mm.; it gave prisms, m. p. 139°, when rubbed with acetone (Found: C, 60·8; H, 7·7; N, 7·1. $C_{10}H_{15}O_3N$ requires C, 60·9; H, 7·6; N, 7·1%).

Similar methods were used for preparation of the following, only method (*a*) (above) being used for the original esters:

Methyl α-benzylamino-γ-methylvalerate, b. p. 81—82°/10^{-4} mm. (Found: C, 71·7; H, 8·3; N, 6·4. $C_{14}H_{21}O_2N$ requires C, 71·5; H, 9·0; N, 6·0%); *hydrochloride*, needles (from ethanol–ether), m. p. 136° (Found: C, 62·4; H, 7·9; N, 5·4. $C_{14}H_{22}O_2NCl$ requires C, 61·9; H, 8·1; N, 5·2%).

Dimethyl N-*benzyl*-N-(1-*carbomethoxy*isoa*myl*)*aminomethylenesuccinate* (I*b*) (yield, 72%), b. p. 150°/3 × 10^{-3} mm. (Found: C, 63·8; H, 7·0; N, 4·2. $C_{21}H_{29}O_6N$ requires C, 64·4; H, 7·4; N, 3·6%).

1-*Benzyl*-2-iso*butyl*-4: 5-*dicarbomethoxy*-3-*hydroxypyridinium chloride* (II*b*) (yield, 34%), prisms, m. p. 130° (decomp.), from ethanol–ether (Found: C, 60·4; H, 6·3; N, 3·8. $C_{20}H_{24}O_5NCl$ requires C, 61·0; H, 6·1; N, 3·6%).

Dimethyl 2-iso*butyl*-3-*hydroxypyridine*-4: 5-*dicarboxylate* (III*b*) (yield, 82%), prisms from aqueous-ethanol (Found: C, 58·4; H, 6·4; N, 5·7. $C_{13}H_{17}O_5N$ requires C, 58·4; H, 6·4; N, 5·2%).

2-iso*Butyl*-3-*hydroxy*-4: 5-*bishydroxymethylpyridine* (IV*b*).—This pyridoxine *analogue* had m. p. 134° (Found: C, 62·5; H, 7·8; N, 7·1. $C_{11}H_{17}O_3N$ requires C, 62·5; H, 8·1; N, 6·6%); *hydrochloride*, needles (from ethanol), m. p. 210° (decomp.) (Found: C, 53·1; H, 6·9; N, 5·6. $C_{11}H_{18}O_3NCl$ requires C, 53·3; H, 7·3; N, 5·7%).

Methyl α-*benzylaminophenylacetate*, b. p. 135—140°/10^{-4} mm. (Found: C, 75·6; H, 6·8; N, 5·3. $C_{16}H_{17}O_2N$ requires C, 75·3; H, 6·7; N, 5·5%).

Dimethyl N-*benzyl*-N-(α-*carbomethoxybenzyl*)*aminomethylenesuccinate* (I*c*), b. p. 125°/2 × 10^{-3} mm. (yield, 73%), needles (from ethanol), m. p. 83° (Found: C, 67·5; H, 6·1; N, 3·6. $C_{23}H_{25}O_6N$ requires C, 67·1; H, 6·1; N, 3·4%).

1-*Benzyl*-4: 5-*dicarbomethoxy*-3-*hydroxy*-2-*phenylpyridinium Chloride* (II*c*).—The cyclisation of (I*c*) was carried out in benzene with sodium ethoxide instead of with sodium, but otherwise the preparation was the same as that of (II*a*) (yield of crude chloride, 64%). The *picrate* corresponding with (II*c*) gave yellow needles, m. p. 165°, from ethanol (Found: C, 55·9; H, 3·8; N, 9·8. $C_{28}H_{22}O_{12}N_4$ requires C, 55·5; H, 3·6; N, 9·2%).

Dimethyl 3-*Hydroxy*-2-*phenylpyridine*-4: 5-*dicarboxylate* (III*c*).—Hydrogenation of (II*c*) gave pale yellow leaflets, m. p. 89° (from light petroleum containing a trace of ethanol) (yield, 74%). The *picrate* of (III*c*) gave yellow leaflets (from ethanol), m. p. 202° (Found: C, 48·6; H, 3·1; N, 11·1. $C_{21}H_{16}O_{12}N_4$ requires C, 48·9; H, 3·1; N, 10·9%). The *acid* was prepared by hydrolysing (III*c*) with baryta; it gave leaflets, m. p. 244°, from water (Found: C, 60·4; H, 3·7; N, 5·5. $C_{13}H_{19}O_5N$ requires C, 60·2; H, 3·5; N, 5·4%).

Dimethyl 3-*Methoxy*-2-*phenylpyridine*-4: 5-*dicarboxylate*.—The ester (III*c*) (18 g.) in ether (100 c.c.) was treated with diazomethane in ether, prepared from nitrosomethylurea (20·6 g.); after 2 days, large, pale yellow prisms had separated. After evaporation, the residue crystallised from aqueous acetic acid as prisms (16·5 g., 84%), m. p. 109°, of the *methoxy*-ester (Found: C, 63·8; H, 5·0; N, 5·1. $C_{16}H_{15}O_5N$ requires C, 63·8; H, 5·0; N, 4·7%).

3-*Methoxy*-2-*phenylpyridine*-4: 5-*dicarboxyamide*.—The above methylated product (16·5 g.) was heated with methanolic ammonia (250 ml., saturated at 0°) at 60° during 24 hr. in an autoclave. The white crystalline *diamide* (11·5 g., 77%) crystallised from methanol containing a few drops of light petroleum (b. p. 60—80°); it had m. p. 224° (decomp.) (Found: C, 61·4; H, 4·9; N, 15·6. $C_{14}H_{13}O_3N_3$ requires C, 62·0; H, 4·8; N, 15·5%).

4: 5-*Dicyano*-3-*methoxy*-2-*phenylpyridine*.—The above diamide (11·5 g.) was added in portions, with stirring, to a mixture of pyridine (42 c.c.), benzene (21 c.c.), and phosphoryl chloride (12·9 g.) at 40°. The temperature was then raised to 65—70°, and the mixture stirred during 1 hr., cooled, and decomposed with ice (50 g.). After evaporation under reduced pressure from a bath at 40° to about 50 ml. (when frothing became troublesome) and cooling, the solid product was collected and dried: sublimation from a bath at 100° at 5 × 10^{-3} mm. gave colourless prisms, m. p. 128°, of the *dicyano*-compound (6·0 g., 60%) (Found: C, 71·5; H, 3·8; N, 17·6. $C_{14}H_9ON_3$ requires C, 71·4; H, 3·9; N, 17·9%).

4: 5-*Bisaminomethyl*-3-*methoxy*-2-*phenylpyridine Trihydrochloride*.—The above dinitrile (0·25 g.) was dissolved in a mixture of methanol (40 ml.) and water (2 ml.), and concentrated hydrochloric acid (0·5 ml.) was added with cooling. This solution was added to reduced Adams' palladium oxide (0·05 g.) in methanol (8 ml.) and water (2 ml.). After hydrogenation at atmospheric pressure, the catalyst was removed and the filtrate evaporated to about 3 ml. under reduced pressure at 50—60° in an atmosphere of nitrogen. Addition of absolute ethanol (10 ml.) and a little ether gave a crystalline product which was washed with dry ethanol (2 ml.). Crystallisation from aqueous ethanol–ether gave the *trihydrochloride* in plates (0·11 g., 30%), m. p. 198° (decomp.) (Found: C, 45·4; H, 6·3; N, 11·5. $C_{14}H_{20}ON_3Cl_3,H_2O$ requires C, 45·4; H, 6·0; N, 11·3%).

4: 5-*Bisaminomethyl*-3-*hydroxy*-2-*phenylpyridine Trihydrobromide*.—A mixture of the above trihydrochloride (1 g.) with aqueous hydrobromic acid (*d* 1·5; 8 ml.) was boiled gently under reflux during 2 hr. The solution was evaporated to dryness under reduced pressure at 85°, and

the residue cooled, triturated with dry acetone (10 ml.), and filtered. The washings were evaporated to about 2 ml. and cooled to obtain a further quantity of the trihydrobromide. The material thus obtained (1·06 g., 79%) was used directly for the next stage without further purification.

3-Hydroxy-4 : 5-bishydroxymethyl-2-phenylpyridine Hydrochloride.—(*a*) The above product (1·06 g.) in water (12 ml.) was stirred with an excess of moist silver chloride (freshly precipitated from 1·3 g. of silver nitrate) during 1 hr. at 90—100°. The solution was filtered hot and the residue washed with 0·1N-hydrochloric acid (1·5 ml.); the combined filtrates were then treated with 2N-hydrochloric acid (18 ml.). This solution was stirred at 30° and treated with a solution of sodium nitrite (0·37 g.) in water (5 ml.), then heated rapidly to 90—100° and kept at that temperature for 20 min. The solution was evaporated under reduced pressure from a bath at 50°, and the residue dried by distillation with benzene, extracted with boiling ethanol (3 × 10 ml.), and filtered hot from sodium chloride. The first extract on cooling deposited prisms (0·14 g.) of m. p. 185°. The filtrate from this was combined with the other two extracts, evaporated under reduced pressure to about 10 ml., and filtered hot. On cooling a further quantity (0·09 g.) of the same material was deposited (yield, 0·23 g., 38%). This material was recrystallised from alcohol without change of m. p., and proved to be identical (by mixed m. p.) with the product obtained by lithium aluminium hydride reduction (see below).

(*b*) Dimethyl 3-hydroxy-2-phenylpyridine-4 : 5-dicarboxylate (2 g.) in ether (60 ml.) was added dropwise with stirring to a solution of lithium aluminium hydride (0·44 g.) in ether (10 ml.). The mixture was stirred for 10 min. after the addition was complete, excess of the reagent was destroyed by the addition of water, and the mixture was then shaken for 5 min. with sulphuric acid (10%; 15 ml.). Sodium hydroxide solution (10%) was then added to bring the solution to pH 7, and the aqueous layer was continuously extracted with ether (100 ml.) during 14 hr. Oil which separated from the ethereal extract was dried in a desiccator, then dissolved in a little dry alcohol and treated with gaseous hydrogen chloride to give a crystalline precipitate. The ethereal extract was dried (Na_2SO_4), filtered, and treated with gaseous hydrogen chloride to give an oil which crystallised when scratched. The crystals were collected and recrystallised from alcohol, to give prisms (1 g., 54%), m. p. 185°, of the *hydrochloride* of (IV*c*) (Found: C, 58·2; H, 5·2; N, 5·0. $C_{13}H_{14}O_3NCl$ requires C, 58·3; H, 5·3; N, 5·2%).

One of us (H. D.) is indebted to the Department of Scientific and Industrial Research for a Maintenance Grant.

University Chemical Laboratory, Cambridge. [*Received, February 5th,* 1953.]

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286. *αβ-Unsaturated Aldehydes and Related Compounds. Part III.* The Addition of Alcohols to the Dimers of Acraldehyde and α-Methylacraldehyde.†*

By R. H. Hall.

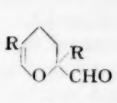
Acid-catalysed reaction of the cyclic dimer of acraldehyde with methanol or ethanol gives the corresponding 6-alkoxy-2-dialkoxymethyltetrahydropyran in good yield. Application of the method to the cyclic dimer of α-methylacraldehyde results, however, in a mixture which contains the 7-alkoxy-1 : 4-dimethyl-6 : 8-dioxa*bicyclo*[3 : 2 : 1]octane, the 6-alkoxy-2-dialkoxymethyltetrahydropyran, and, in most instances, the 6-alkoxy-2-formyltetrahydro-2 : 5-dimethylpyran, the alkoxy-groups in each case being derived from the alcohol employed.

The acid-catalysed addition of alcohols to dihydropyrans to give 2-alkoxytetrahydropyrans is well known (cf. Paul, *Bull. Soc. chim.*, 1934, **1**, 973; Woods and Kramer, *J. Amer. Chem. Soc.*, 1947, **69**, 2246); it has indeed been used as a method for protecting alcohol groups since the alcohol can readily be recovered by acid hydrolysis of the adduct (Parham and Anderson, *ibid.*, 1948, **70**, 4187). This paper describes the application of the addition reaction to the cyclic dimers of acraldehyde and α-methylacraldehyde, 2-formyl-3 : 4-

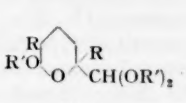
* Part II, *J.*, 1942, 4083. † Part of this work has been described in B.P. Appl. 31,846/49.

dihydropyran (I; R = H) and 2-formyl-3 : 4-dihydro-2 : 5-dimethylpyran (I; R = Me), respectively.

From the reaction of acraldehyde dimer (I; R = H) with methanol or ethanol in the presence of anhydrous hydrogen chloride at temperatures of 0° to atmospheric, the corresponding 6-alkoxy-2-dialkoxymethyltetrahydropyrans (II; R = H, R′ = Me or Et) were obtained in good yields. When the dimer of α-methylacraldehyde (I; R = Me) was subjected to reaction with a large excess of methanol or ethanol, however, the products were more complex: at room temperature methanol gave a poor yield of 2-dimethoxymethyltetrahydro-6-methoxy-2 : 5-dimethylpyran (II; R = R′ = Me), considerable



(I)



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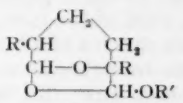

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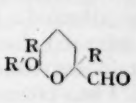

(IV)

amounts of lower-boiling compounds being also obtained; these were shown to contain 7-methoxy-1 : 4-dimethyl-6 : 8-dioxa*bicyclo*[3 : 2 : 1]octane (III; R = R′ = Me) and, in addition, in the majority of cases, 2-formyltetrahydro-6-methoxy-2 : 5-dimethylpyran (IV; R = R′ = Me), which could not be separated from the bicyclic compound by distillation. Precise conditions for avoiding the formation of the formyl compound could not be found, the presence or absence of this material in the products appearing to be fortuitous.

The structure of (III; R = R′ = Me) was established by elementary analysis, lack of reaction with semicarbazide acetate in neutral solution, and infra-red spectroscopic analysis (discussed below) which confirmed the absence of functional groups other than ether groups. The only formula compatible with all these is that shown. While this work was in progress Stoner and McNulty (*J. Amer. Chem. Soc.*, **1950**, **72**, **1531**) reported the preparation of such a compound by the treatment of α-methylacraldehyde dimer with methanol in the presence of calcium chloride as catalyst and somewhat later Whetstone (U.S.P. 2,511,891) described similar work in which hydrogen chloride was used as catalyst; in the latter investigation the amount of methanol employed was restricted to about 2 moles per mole of dimer. Certain of the physical constants recorded by these authors for their products did not agree very closely, however, with those of the material obtained in the present work. These inconsistencies were tentatively ascribed to the stereochemistry of this bicyclic polyether; several stereoisomers were obviously possible and these may have been interconverted, at least partly, on attempted fractionation. In partial confirmation it was found that material made by Whetstone's method (*loc. cit.*) had a refractive index significantly different from that obtained in the earlier work reported here; nevertheless, the two compounds had very similar infra-red absorption spectra (see below). The products were obviously of the same type, but not identical.

2-Formyltetrahydro-6-methoxy-2 : 5-dimethylpyran (IV; R = R′ = Me) was characterised as its semicarbazone but could not be obtained pure; regeneration from the semicarbazone was not attempted in view of the known instability of 2-alkoxytetrahydropyrans towards acids (Parham and Anderson, *loc. cit.*). The structure assigned to the formyl compound was based on analysis of the semicarbazone which showed that the parent carbonyl compound was derived from one mol. of 2-formyl-3 : 4-dihydro-2 : 5-dimethylpyran (I; R = Me) and one mol. of methanol. The formyl compound was probably an intermediate in the formation of 2-dimethoxymethyltetrahydro-6-methoxy-2 : 5-dimethylpyran (II; R = R′ = Me); the other likely intermediate, namely, the dimethyl acetal of 2-formyl-3 : 4-dihydro-2 : 5-dimethylpyran, was not detected in the reaction products.

Replacement of methanol by ethanol in the reaction with 2-formyl-3 : 4-dihydro-2 : 5-dimethylpyran (I; R = Me) gave similar results although the yield of 2-diethoxymethyl-6-ethoxytetrahydro-2 : 5-dimethylpyran (II; R = Me, R′ = Et) was extremely poor. 7-Ethoxy-1 : 4-dimethyl-6 : 8-dioxa*bicyclo*[3 : 2 : 1]octane (III; R = Me, R′ = Et) and 6-ethoxy-2-formyltetrahydro-2 : 5-dimethylpyran (IV; R = Me, R′ = Et) were both

present in the lower-boiling products; the former was isolated in pure condition in some experiments and on one occasion in two, apparently stereoisomeric, forms. 6-Ethoxy-2-formyltetrahydro-2 : 5-dimethylpyran (IV; R = Me, R′ = Et) was characterised as its semicarbazone but, as in the case of the corresponding 6-methoxy-compound (IV; R = R′ = Me), was not obtained pure.

In order to prepare reasonable quantities of 2-diethoxymethyl-6-ethoxytetrahydro-2 : 5-dimethylpyran (II; R = Me, R′ = Et), the crude product from the low-temperature reaction of 2-formyl-3 : 4-dihydro-2 : 5-dimethylpyran (I; R = Me) with ethanol containing hydrogen chloride was mixed with methylene dichloride and submitted to azeotropic distillation to remove water. Neutralisation of the anhydrous material, followed by fractionation, afforded a 37% yield of the pure compound (II; R = Me, R′ = Et).

The infra-red absorption spectra of all compounds of type (III) obtained as above did not contain any bands due to carbonyl or hydroxyl groups. A very intense band near 1100 cm.$^{-1}$ was present in each case; this, in the absence of carbonyl and hydroxyl groups, was good evidence for the presence of ether linkages. The spectra also had strong bands in the region 920—980 cm.$^{-1}$ which, by analogy with the spectra of paraldehyde, dioxan, tetrahydropyran, etc., suggested that at least one ether group was part of a saturated ring system.

Experimental

2-Formyl-3 : 4-dihydropyran (I; R = H).—Acraldehyde dimer was prepared from freshly distilled acraldehyde by the method of Sherlin, Berlin, Serebrennikova, and Rabinovich (*J. Gen. Chem., U.S.S.R.*, 1938, **8**, 22; cf. Alder and Rüden, *Ber.*, 1941, **74**, 920). The pure material had b. p. 40°/10·5 mm., 47·5°/15 mm., n_D^{20} 1·463 (Sherlin *et al.*, *loc. cit.*, give b. p. 40—40·5°/10 mm., 44°/13 mm., n_D^{20} 1·4660), and changed during a few days to a transparent resin; it was therefore used immediately it had been distilled. The semicarbazone had m. p. 119—120° (Sherlin *et al.*, *loc. cit.*, give m. p. 123°), and the dimedone *derivative* (from aqueous ethanol) m. p. 143—144° (Found: C, 70·15; H, 8·25. $C_{22}H_{30}O_5$ requires C, 70·55; H, 8·05%). A portion, hydrogenated in ethanol over Raney nickel until two mols. had been absorbed, furnished tetrahydro-2-hydroxymethylpyran, b. p. 73—74·5°/11 mm., 181—182°/760 mm., n_D^{17} 1·4583 (Soc. des Usines Chimiques Rhone-Poulenc, B.P. 595,379, give b. p. 184—186°, $n_D^{24·5}$ 1·4565; Helberger, Ulubay, and Civelekoglu, *Annalen*, 1949, **561**, 215, give b. p. 70—72°/12 mm.); this gave a 3 : 5-*dinitrobenzoate*, which separated from 95% ethanol in needles, m. p. 84—85° (Found: C, 50·3; H, 4·75; N, 8·7. $C_{13}H_{14}O_7N_2$ requires C, 50·3; H, 4·55; N, 9·05%), and a *hydrogen* 3-*nitrophthalate*, m. p. 163—164° (Found: C, 54·5; H, 4·85; N, 4·95. $C_{14}H_{15}O_7N$ requires C, 54·35; H, 4·9; N, 4·55%), from ethanol.

2-Formyl-3 : 4-dihydro-2 : 5-dimethylpyran (I; R = Me).—The dimer of α-methylacraldehyde was prepared by refluxing the parent aldehyde at atmospheric pressure for several days, recovering unchanged monomer by distillation at atmospheric pressure, and distilling the residual dimer *in vacuo* (cf. Stoner and McNulty, *loc. cit.*). Pure 2-formyl-3 : 4-dihydro-2 : 5-dimethylpyran had b. p. 58°/13 mm., n_D^{20} 1·4533 (Schulz and Wagner, *Angew. Chem.*, 1950, **62**, 105, give b. p. 55—56°/12 mm.; Stoner and McNulty, *loc. cit.*, give n_D^{20} 1·454; Shell Development Co., U.S.P. 2,479,283, gives n_D^{20} 1·4537). Its semicarbazone had m. p. 175—176° (Rohm and Haas Co., U.S.P. 2,473,497, and Shell Development Co., *loc. cit.*, give m. p. 174—177° and 177°, respectively).

Reaction of Acraldehyde Dimer with Ethanol.—A solution of anhydrous hydrogen chloride (1·25 g.) in absolute ethanol (50 ml.) was added slowly to a stirred, cooled solution of (I; R = H) (47 g.) in absolute ethanol (200 ml.) at 0—4°. The resultant mixture was stirred and kept at 0° for 1 hr., then allowed to warm gradually to room temperature and kept for 40 hr.

The product was made just alkaline to litmus by the cautious addition of ethanolic sodium ethoxide solution below 3°, and then a slight excess of glacial acetic acid was added. The filtered mixture was evaporated *in vacuo* and the crude product distilled without a column. Subsequent fractionation of the distillate (81·0 g.), b. p. 80—130°/11 mm., afforded pure 2-*diethoxymethyl-6-ethoxytetrahydropyran* (62·6 g., 63%), b. p. 114—117°/9 mm., n_D^{20} 1·4330 (Found: C, 61·95; H, 10·25. $C_{12}H_{24}O_4$ requires C, 62·05; H, 10·4%).

Reaction of Acraldehyde Dimer with Methanol.—A solution of anhydrous hydrogen chloride (1·42 g.) in methanol (50 ml.) was added during 30 min. to a stirred, cooled solution of (I; R = H) (59 g.) in methanol (236 ml.) at 0—4°. The resultant mixture was stirred below 4° for

a further 30 min. and then kept at room temperature for some hr. Isolation of the product as described above afforded pure **2-*dimethoxymethyltetrahydro*-6-*methoxypyran*** (71·5 g., 71%), b. p. 93—96°/10 mm., n_D^{20} 1·4369 (Found: C, 57·15; H, 9·45. $C_9H_{18}O_4$ requires C, 56·8; H, 9·55%).

Reaction of α-Methylacraldehyde Dimer with Methanol.—(*a*) Addition of (I; R = Me) (53 g.) to methanol (60 ml.) resulted in the spontaneous evolution of heat. The cooled solution was added dropwise, below 4°, to a stirred solution of anhydrous hydrogen chloride (0·236 g.) in methanol (170 ml.), and the mixture kept in ice for some hr. and then at room temperature for several days. The product was made alkaline to litmus by means of methanolic sodium methoxide, a slight excess of acetic acid added, and the mixture distilled *in vacuo*. After removal of methanol, material (65·1 g.) was collected (boiling range 75—120°/9—10 mm.), which on subsequent fractionation afforded the following main fractions: (i) b. p. 80—82°/10 mm. (14·55 g.), n_D^{20} 1·4500 (Found: C, 63·1, 63·05; H, 9·2, 9·3. Calc. for $C_9H_{16}O_3$: C, 62·75; H, 9·35%), and (ii) **2-*dimethoxymethyltetrahydro*-6-*methoxy*-2 : 5-*dimethylpyran*** (26·05 g.), b. p. 101—102°/10 mm., n_D^{20} 1·4399, d_4^{20} 1·0063 (Found: C, 60·25, 60·3; H, 10·1, 10·3%; $[R]_D^{20}$ 57·16. $C_{11}H_{22}O_4$ requires C, 60·5; H, 10·15%; $[R]_D^{20}$ 57·37).

Fraction (i) was probably 7-methoxy-1 : 4-dimethyl-6 : 8-dioxa*bicyclo*[3 : 2 : 1]octane (see p. 1399). Stoner and McNulty (*loc. cit.*) give b. p. 125°/100 mm., n_D^{20} 1·445, and Whetstone (*loc. cit.*) gives b. p. 66—66·5°/9·5 mm. for this compound.

Most experiments, under the same or slightly different conditions, gave low-boiling fractions, *e.g.*, b. p. 82·5—83·5°/12 mm., n_D^{20} 1·4417, which contained, in addition to the bicyclic compound, an isomeric carbonyl compound [Found (for the fraction): C, 63·5, 62·6; H, 9·55, 9·3. $C_9H_{16}O_3$ requires C, 62·75; H, 9·35%]. A *semicarbazone*, prepared from such a fraction in neutral solution, had m. p. 211° (from ethyl acetate) (Found: C, 52·65; H, 8·15; N, 18·3. $C_{10}H_{19}O_3N_3$ requires C, 52·4; H, 8·35; N, 18·3%). The carbonyl compound was thus **2-*formyltetrahydro*-6-*methoxy*-2 : 5-*dimethylpyran***.

(*b*) (cf. Whetstone, *loc. cit.*) Methanolic hydrogen chloride (1·2 ml.; 0·5N) was added below 40° to a stirred, cooled, solution of (I; R = Me) (56 g.) in methanol (32 ml.). The resultant mixture was kept at 39—40° for 1 hr., cooled, neutralised with calcium carbonate (1 g.), stirred for ½ hr., filtered, and finally fractionated. A fraction (11·55 g.), b. p. 70°/12 mm. (Whetstone, *loc. cit.*, gives b. p. 66—66·5°/9·5 mm.), n_D^{20} 1·4414 (Found: C, 62·95; H, 9·6. Calc. for $C_9H_{16}O_3$: C, 62·75; H, 9·35%), was obtained which appeared to be a stereoisomer of the 7-methoxy-1 : 4-dimethyl-6 : 8-dioxa*bicyclo*[3 : 2 : 1]octane obtained as in (*a*).

Reaction of α-Methylacraldehyde Dimer with Ethanol.—(*a*) Addition of (I; R = Me) (70 g.) to ethanol (70 ml.) resulted in the spontaneous evolution of heat. The cooled mixture was added, below 3°, to a stirred solution of anhydrous hydrogen chloride (0·314 g.) in ethanol (205 ml.) which had previously been cooled below 2° and the resultant solution was kept at room temperature for several hr. Ethanolic sodium ethoxide was added cautiously to the mixture until it was just alkaline to litmus. A slight excess of acetic acid was then introduced and the solvent evaporated *in vacuo*. The crude product was filtered to remove inorganic salts, then distilled, and the distillate (61·7 g.), b. p. 75—110°/9·5 mm., fractionated, giving three main fractions: (i) b. p. 75·5—79°/10 mm. (17·0 g.), n_D^{20} 1·4380 (Found: C, 64·1, 64·25; H, 9·95, 9·65. $C_{10}H_{18}O_3$ requires C, 64·5; H, 9·75%); (ii) b. p. 87·5—89°/10 mm. (28·0 g.), n_D^{20} 1·4469 (Found: C, 64·35; H, 9·7%); and (iii) b. p. 119·5—121°/10 mm. (10·75 g.), n_D^{20} 1·4345—1·4388, probably slightly impure 2-diethoxymethyl-6-ethoxytetrahydro-2 : 5-dimethylpyran [see (*b*) below].

By infra-red analysis, fractions (i) and (ii) were shown to be very similar but not identical. Their spectra (see above for details) indicated the absence of carbonyl and hydroxyl groups but strong absorption due to ether groups, probably both in and out of a ring, was observed in each case. The compounds are probably stereoisomers of **7-*ethoxy*-1 : 4-*dimethyl*-6 : 8-*dioxa*bicyclo-[3 : 2 : 1]*octane***.

Most experiments, under the same or slightly different conditions, gave low-boiling fractions, *e.g.*, b. p. 90—90·5°/13 mm., n_D^{20} 1·4390, which contained, in addition to the bicyclic compound, an isomeric carbonyl compound [Found (for fraction): C, 64·45; H, 9·55. $C_{10}H_{18}O_3$ requires C, 64·5; H, 9·75%). A *semicarbazone*, prepared in neutral solution, formed needles, m. p. 223—224°, from aqueous ethanol (Found: C, 54·25; H, 8·6; N, 17·3. $C_{11}H_{21}O_3N_3$ requires C, 54·3; H, 8·7; N, 17·25%). Hence the carbonyl compound was most probably **6-*ethoxy*-2-*formyltetrahydro*-2 : 5-*dimethylpyran***.

(*b*) A solution of (I; R = Me) (70 g.) in ethanol (85 ml.) was added below 20° to ethanol (203 ml.) containing anhydrous hydrogen chloride (1·44 g.) which was cooled in ice. Methylene

dichloride (250 ml.) was then introduced and the mixture distilled through a 3-ft. Vigreux column fitted with a phase-separating still-head which decanted the upper layer in the distillate continuously and returned the lower layer to the column as reflux.

After 44 hr.' heating, the product was cooled, made just alkaline to litmus with ethanolic sodium ethoxide, and then just neutral with acetic acid. After removal of solvents the product was distilled *in vacuo*. Subsequent fractionation of the distillate afforded pure 2-*diethoxymethyl*-6-*ethoxytetrahydro*-2 : 5-*dimethylpyran* (48·5 g., 37%), b. p. 125—125·5°/12 mm., n_D^{20} 1·4332 (Found : C, 65·05; H, 10·7. $C_{14}H_{28}O_4$ requires C, 64·6; H, 10·85%).

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THE DISTILLERS CO. LTD., RESEARCH AND DEVELOPMENT DEPT.,
GREAT BURGH, EPSOM, SURREY. [*Received, December 9th*, 1952.]

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287. *The Oxidation of Hydrazine in Aqueous Solution. Part II.* The Use of* ^{15}N *as a Tracer in the Oxidation of Hydrazine.*

By W. C. E. HIGGINSON and D. SUTTON.

The isotopic composition of nitrogen evolved in the oxidation of hydrazine containing 33 atom % of ^{15}N in the presence of a large excess of ordinary hydrazine has yielded information as to the extent of N–N bond fission in oxidation. As suggested in the preceding paper, oxidation by 1-electron-transfer oxidising agents and complex oxidising agents involves the simultaneous occurrence of two limiting reactions :

$$N_2H_4 \xrightarrow{-(e)} \tfrac{1}{2}N_2 + NH_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$N_2H_4 \xrightarrow{-4(e)} N_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

In (1) the nitrogen atoms in half the evolved nitrogen molecules are derived from the same hydrazine molecule; in the other half the nitrogen atoms come from separate hydrazine molecules. In (2), which is also the sole reaction for 2-electron-transfer oxidation and for all oxidations in alkaline solution, no N–N fission occurs and no new N–N bonds are formed.

The nature of some of the radical intermediates is discussed.

THE reaction schemes for the oxidation of hydrazine in acid, aqueous solution discussed in Part I* can be confirmed to some extent by a study of the isotopic composition of the nitrogen formed in the oxidation of hydrazine enriched in ^{15}N. We have synthesised hydrazine from ammonia containing 33·4 atom % of ^{15}N. This hydrazine was assumed to contain the statistical proportions of $^{15}N_2H_4$, $^{15}NH_2{\cdot}^{14}NH_2$, and $^{14}N_2H_4$ in accordance with the expression $[^{15}NH_2{\cdot}^{14}NH_2]^2/([^{15}N_2H_4][^{14}N_2H_4]) = 4$. In dilute sulphuric acid this hydrazine was diluted with ordinary hydrazine sulphate (N_2H_4,H_2SO_4), the molar ratio of ^{15}N-enriched : ordinary hydrazine being 1 : 92·0. In this mixture the proportions of $^{15}N_2H_4$, $^{15}NH_2{\cdot}^{14}H_2$, and $^{14}N_2H_4$ no longer correspond to those of statistical equilibrium. The hydrazine sulphate mixture was then oxidised by an excess of various oxidising agents and the evolved nitrogen collected in each case and submitted to mass-spectroscopic analysis for the 28, 29, and 30 mass-number abundances (measured as the ratios 30 : 29 and 29 : 28). These abundance ratios for those reagents which react according to the equation $N_2H_4 \xrightarrow{-4(e)} N_2$ are recorded in Table 1. The abundance ratios

* Part I, *J.*, 1953, 1380.

and observed consumption of oxidising agent in equivalents per hydrazine molecule oxidised are recorded in Table 2 for other oxidising agents.

TABLE 1.

Reagent	Conditions	Isotope abundance ratios 30 : 29	29 : 28	^{15}N (%)
IO_3^-	0·1N-H_2SO_4	0·1022 ± 0·0003	0·01192 ± 0·00004	0·708
		0·1036 ± 0·0005	0·01197 ± 0·00002	0·714
Tl(III)	0·7N-$HClO_4$	0·1025 ± 0·0006	0·01208 ± 0·00005	0·718
$Fe(CN)_6^{3-}$	0·1N-NaOH	0·1026 ± 0·0005	0·01252 ± 0·00004	0·744
		0·1016 ± 0·0006	0·01196 ± 0·00007	0·710

If on quantitative oxidation of hydrazine to nitrogen, no fission of the N–N bonds occurs, the abundance ratios should be equal to those calculated for the hydrazine mixture, *i.e.*, 30 : 29 = 0·0987, 29 : 28 = 0·01247, ^{15}N = 0·736 atom %. If all the N–N bonds are broken in the oxidation, the statistical proportions of $^{15}N_2$, $^{15}N^{14}N$, and $^{14}N_2$ will be formed, and the abundance ratios can be calculated from the proportion of ^{15}N present (0·736 atom % as before) as 30 : 29 = 0·00371, 29 : 28 = 0·01482. Comparison shows that there is fairly good agreement between the experimental values and those calculated on the assumption that no N–N bond fission occurs. Exact agreement is not to be expected since isotope fractionation is likely to occur during the synthesis of the ^{15}N-enriched hydrazine; analysis of the nitrogen formed as by-product during the synthesis showed 32·85 atom % of ^{15}N instead of the 33·4 atom % of the ammonia used. Further, we have assumed that the nitrogen isotopes are distributed in ordinary hydrazine in exactly the statistical equilibrium proportions and that the amount of ^{15}N present is the same as in atmospheric nitrogen, 0·38 atom % (Vaughan, Williams, and Tate, *Phys. Review*, 1934, **46**, 327). We therefore feel justified in assuming that, under conditions where elementary nitrogen is the sole nitrogenous oxidation product, no fission of the N–N bond occurs.

In the experiments listed in Table 2, comparison with Table 1 shows that the proportion of $^{15}N_2$ has decreased while that of $^{15}N^{14}N$ has increased, the differences being more marked the lower the stoicheiometry. This suggests that whenever less than four equivalents of oxidising agent are consumed per N_2H_4 molecule oxidised, that is, whenever ammonia is formed, some of the nitrogen is formed by a mechanism involving the union of

TABLE 2.

Reagent	Conditions	Equivs. per N_2H_4	Isotope abundance ratios 30 : 29	29 : 28	^{15}N (%)
Ce(IV)	0·5N-H_2SO_4	1·06	0·0499 ± 0·0007	0·01327 ± 0·00003	0·738
Ce(IV)	0·5N-H_2SO_4	1·38	0·0580 ± 0·0004	0·01298 ± 0·00004	0·729
Fe(III)	N-H_2SO_4; 4 hr. at 80°	1·49	0·0607 ± 0·0004	0·01293 ± 0·00004	0·723
Fe(III)	N-H_2SO_4; 4 hr. at 80°	1·76	0·0685 ± 0·0006	0·01271 ± 0·00007	0·725
V(V)	N-H_2SO_4	3·66	0·1009 ± 0·0011	0·01134 ± 0·00006	0·673
V(V)	N-H_2SO_4	3·92	0·1018 ± 0·0006	0·01189 ± 0·00004	0·706
$KMnO_4$	0·05N-H_2SO_4	2·11	0·0742 ± 0·0029	0·01200 ± 0·00010	0·680
$K_2Cr_2O_7$	0·1N-H_2SO_4	3·82	0·0970 ± 0·0003	0·01140 ± 0·00004	0·672

nitrogen-containing radicals from two different hydrazine molecules. By linear extrapolation of plots of the 30 : 29 and 29 : 28 abundance ratios against the corresponding stoicheiometry for the experiments with Ce(IV) and Fe(III), the 30 : 29 and 29 : 28 ratios at 1 equivalent of oxidising agent consumed per N_2H_4 molecule may be estimated as 0·0490 and 0·01331 respectively. These values do not correspond to complete fission of the N–N bonds in hydrazine. We have therefore assumed that a part of the nitrogen produced under the conditions of the limiting equation $N_2H_4 \xrightarrow{-(e)} \frac{1}{2}N_2 + NH_3$ involves no N–N fission and therefore has the same distribution of ^{15}N isotopes as the hydrazine mixture. The other part is assumed to involve complete N–N fission, and the nitrogen isotope distribution will be statistical. Calculation based on the ^{15}N-isotope distribution in the hydrazine mixture and in the nitrogen produced at a stoicheiometry of 1 equivalent of oxidising agent per N_2H_4 molecule consumed then shows that 0·508 of the total nitrogen

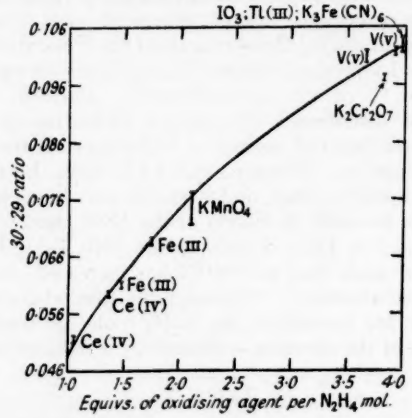
is formed, molecule for molecule, from a single hydrazine molecule, while the remaining part derives one nitrogen atom from each of two hydrazine molecules. Within the errors of the quantities used in the calculation this corresponds to the formation of half the total nitrogen from a single hydrazine molecule and half from two hydrazine molecules.

In the actual cases studied the stoicheiometry lay between 1 and 4, and, as suggested in the preceding paper, even for complex oxidising agents such as potassium permanganate, this can be ascribed to the simultaneous occurrence of the two reactions:

$$N_2H_4 \xrightarrow{-(e)} \tfrac{1}{2}N_2 + NH_3$$

$$N_2H_4 \xrightarrow{-4(e)} N_2$$

From the consumption of oxidising agent, the proportion of each reaction can be determined. The isotopic composition of the nitrogen evolved for any stoicheiometry between 1 and 4 can thus be calculated as our results have already shown the connection between the isotopic composition of the evolved nitrogen and of the parent hydrazine in each of the two limiting reactions above. For this purpose we have assumed that the isotopic abundance ratios in the hydrazine mixture are given by the average of the first three experiments



listed in Table 1, *i.e.*, $30 : 29 = 0{\cdot}1028$, $29 : 28 = 0{\cdot}01199$, $^{15}N = 0{\cdot}713$ atom %. The calculated 30 : 29 abundance ratio, plotted as a curve against the equivalents of oxidising agent consumed per hydrazine molecule (see Figure), holds only when an excess of oxidising agent is used so that isotope fractionation effects are minimised. The figure also shows the experimental values for the reagents in Table 2. Agreement is reasonably good and thus the validity of regarding the oxidation at a consumption of oxidising agent of less than four equivalents per hydrazine molecule as involving two distinct series of reactions seems confirmed. The series giving nitrogen only will, as with the 2-electron-transfer mechanism, involve the intermediate formation of N_2H_2, though here two steps are necessary:

$$N_2H_4 \xrightarrow{-(e)} N_2H_3 \xrightarrow{-(e)} N_2H_2 \dashrightarrow N_2$$

In alkaline solution 1-electron-transfer reagents presumably react solely according to this scheme. In the case of complex oxidising agents such as potassium permanganate and dichromate 2-electron-transfer steps leading directly to N_2H_2 may also occur.

The second series of reactions has, we have suggested, the same initial step as the first series for 1-electron-transfer reagents, and then the N_2H_4 radicals formed dimerise and eventually break down to nitrogen and ammonia. This step seems to occur in acid solution only:

$$N_2H_4 \xrightarrow{-(e)} N_2H_3 \longrightarrow \tfrac{1}{2}N_4H_6 \dashrightarrow \tfrac{1}{2}N_2 + NH_3$$

The observation that half of the nitrogen evolved in this series of reactions is formed from two hydrazine molecules and half from one hydrazine molecule suggests that the above schemes can be written in greater detail:

$$H_2\overset{a}{N}-\overset{a}{N}H_2 + H_2\overset{b}{N}-\overset{b}{N}H_2 \longrightarrow H_2\overset{a}{N}-\overset{a}{N}H\cdot + \cdot H\overset{b}{N}-\overset{b}{N}H_2 \longrightarrow$$

$$H_2\overset{a}{N}-\overset{a}{N}H-\overset{b}{N}H-\overset{b}{N}H_2 \longrightarrow \overset{a}{N}H_3 + H\overset{a}{N}=\overset{b}{N}-\overset{b}{N}H_2 \rightleftharpoons H_2\overset{a}{N}-\overset{b}{N}=\overset{b}{N}H$$

$$H_2\overset{a}{N}-\overset{a}{N}=\overset{b}{N}H + \overset{b}{N}H_3 \rightleftharpoons H\overset{a}{N}=\overset{a}{N}-\overset{b}{N}H_2$$

$$H\overset{a}{N}=\overset{b}{N}-\overset{b}{N}H_2 \longrightarrow \overset{a}{N}\equiv\overset{b}{N} + \overset{b}{N}H_3, \text{ etc.}$$

Here *a* and *b* are merely used to identify the particular hydrazine molecule from which the atoms so marked originate. Thus the intermediate $H_2N\cdot N{:}NH$, as formed, has a nitrogen atom from one hydrazine molecule joined by a double bond to a nitrogen atom from another hydrazine molecule. Loss of ammonia would be expected always to involve loss of the NH_2-group, and the doubly bound nitrogen atoms would remain joined together. Nitrogen molecules so formed, possessing a nitrogen atom from each of two hydrazine molecules, must, it can be shown, exhibit the statistical distribution of the nitrogen isotopes. However if there is an equal possibility of losing either of the terminal nitrogen atoms as ammonia the experimental findings can be explained. We suggest that there can be rapid interconversion by proton transfer, $H_2\overset{a}{N}\cdot\overset{b}{N}{:}\overset{b}{N}H \rightleftharpoons H\overset{a}{N}{:}\overset{b}{N}\cdot\overset{b}{N}H_2$. Possibly the intermediate form $H_2\overset{+}{N}\cdots N\cdots NH_2$ is relatively stable in acid solution, though it is necessary only that the interconversion of the unsymmetrical forms should be rapid compared with the rate of loss of ammonia to account for the experimental findings.

N_3H_3 has been postulated previously in discussions of the oxidation of hydrazine (see, *e.g.*, Audrieth and Ogg, " The Chemistry of Hydrazine," John Wiley and Sons, New York, 1951, p. 127). Dimroth and Pfister (*Ber.*, 1910, **43**, 2757) also suggested that this compound may exist as an unstable intermediate in the reduction of hydrazoic acid, though their evidence appeared inconclusive.

Experimental

Synthesis of Hydrazine from Ammonia Rich in ^{15}N.—Koenig and Brings' synthesis (*Z. phys. Chem.*, Bodenstein-Festband, 1931, 541) was used, in which a silent discharge is passed through ammonia gas which is continually condensed to liquid, removing any hydrazine formed from the discharge zone (see also Sutton, Thesis, Manchester, 1952). The source of enriched ammonia was ammonium nitrate, enriched to 33·4 mole % of ^{15}N in the ammonium-nitrogen only, obtained from A.E.R.E., Harwell. 0·9 G. of ammonia was used and about one-quarter of this was decomposed. The yield of hydrazine was 0·071 g.

Preparation of the Hydrazine Sulphate Mixture.—The ^{15}N-rich hydrazine was dissolved in excess of 0·1N-sulphuric acid, to give a 0·02125M-solution (titration against potassium iodate solution under Andrews' conditions). In this way the yield was found to be 0·0694 g. A portion of this solution of ^{15}N-enriched hydrazine was diluted with a solution in 0·1N-sulphuric acid of " AnalaR " hydrazine hydrogen sulphate (standardised as above), in proportions of one mole of enriched hydrazine to 92·0 moles of ordinary hydrazine. The final hydrazine solution was 0·01973M.

Preparation of Samples of Nitrogen for Mass-spectroscopic Analysis.—A two-bulb reaction vessel was used for the production of nitrogen samples. Each bulb was of 50-ml. capacity, and up to 25 ml. of the hydrazine sulphate mixture or of oxidising agent could be placed in each. The vessel was connected by a flexible stainless steel tube to a Töpler pump whence evolved gas could be compressed into calibrated bulbs for measurement of the volume, and thence into a 5-ml. sample tube for subsequent transference to a mass-spectrometer.

Hydrazine sulphate mixture and excess of oxidising agent were measured by pipette into separate bulbs, acid or alkali was added if required, the solutions were frozen in liquid air, and the vessel evacuated by a mercury-vapour pump. The vessel was then isolated from the pump and immersed in water at 70°, with avoidance of splashing. It was then again immersed in liquid air, and the air which had boiled out of the solution was pumped off. This procedure was repeated, after which the reactants were melted and mixed. Generally the temperature

of mixing was about 18°, but was 80° for oxidation by ferric perchlorate (4 hours to ensure complete reaction). For Fe(III), Ce(IV), and V(V) the stoicheiometry was altered in successive experiments by keeping in one experiment the oxidising agent, and in the other the hydrazine in excess during the initial mixing. Preliminary experiments were necessary in some cases to determine the appropriate time of reaction. After reaction, the whole was cooled in liquid air, and connected with the Töpler pump; one stroke removed about half of the evolved nitrogen which was then compressed into the calibrated measuring bulbs, and the pressure was noted. The gas was next transferred into a sample tube and sealed off for mass-spectroscopic analysis. In most of the experiments at a stoicheiometry of less than 4 the remainder of the evolved nitrogen was pumped off and measured.

The amount of oxidising agent consumed was determined by titration of the excess with an appropriate reducing agent or titration of the amount reduced with an appropriate oxidising agent. In experiments with Ce(IV) and Fe(III) a fairly large amount of ammonia was produced and as a further check on the stoicheiometry this was determined (Kjeldahl) after the consumption of oxidising agent had been found. Comparison between amounts of nitrogen predicted from the stoicheiometry and measured showed fair agreement, the latter being approx. 1·5% low. We estimate that the observed stoicheiometry is accurate within ±0·005 for oxidation by Ce(IV), ± 0·01 for Fe(III) and $KMnO_4$, and ±0·02 for other reagents.

0·1—0·5 Millimole of hydrazine was used, with about a 50% excess of oxidising agent (generally about 0·1M), except for the slow reaction with ferric perchlorate where a 40-fold excess was used. The amounts of nitrogen produced varied from 0·1 to 0·5 millimole, and the samples for analysis from 1 to 2 ml. at N.T.P.

Mass-spectrometric Analysis.—The samples were analysed in a Metropolitan-Vickers Type M.S.2 mass-spectrometer. We are grateful to Messrs. Metropolitan-Vickers Electrical Company Ltd. for their kind co-operation and especially to Dr. Waldron (of their Research Department) for making the measurements and for advice. In addition to the 30 : 29 and 29 : 28 abundance ratios, the proportion of oxygen in most of the samples was determined—several samples contained about 0·6% of oxygen; a few contained over 1% and these results were discarded. We cannot suggest a reason for the presence of this oxygen; the amounts of evolved gas calculated and measured were in sufficiently good agreement to make unlikely the leak of an amount of air necessary to cause the observed oxygen content. On the other hand, the presence or absence of oxygen seemed to bear no relation to the reagent used and we do not think that it can be a by-product of reaction. We therefore assumed a leak of air and corrected the 30 : 29 and 29 : 28 abundance ratios where necessary: the corrections are small—the 30 : 29 ratio is increased by about 1·5% on average—and none of the conclusions drawn would be altered if they were not made.

We acknowledge with gratitude the encouragement and advice received from the late Professor M. G. Evans, F.R.S., in the work described in this and in the preceding paper.

THE UNIVERSITY, MANCHESTER. [*Received, December 17th*, 1952.]

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288. *The Hydrolysis of Acetic Anhydride. Part II.* Catalysis by Pyridine.*

By S. L. BAFNA and V. GOLD.

The hydrolysis of acetic anhydride in acetone–water is strongly catalysed by small amounts of pyridine. The dependence of the reaction velocity on the concentrations of pyridine and acetic anhydride appears complex but is satisfactorily explained if the formation of catalytically inactive pyridinium acetate (by interaction of the catalyst and the product of reaction) is allowed for.

IT is common knowledge that many preparative acylations are facilitated by the presence of alkali, carboxylate ions, or tertiary amines such as pyridine. The mechanism of the catalysis, superficially suggestive of general base catalysis, has not so far been elucidated and only a few isolated kinetic studies of the phenomena have been reported (*e.g.*, Leman,

* Part I, *Trans. Faraday Soc.*, 1948, **44**, 506.

Bull. Soc. chim., **1945**, **12**, 908; **1947**, **14**, 514). The present work deals with the catalysis of the hydrolysis of acetic anhydride by pyridine in 50% acetone–water. The particular choice of solvent is unfortunate in some respects since it necessitates the introduction of an unknown equilibrium constant into the kinetic equations. It was made in order to obtain suitable rates and solubilities in related measurements on the acylation of amines.

Experimental

Solvent Mixtures.—The solvent was made up by weight from distilled water and " AnalaR " acetone, generally without purification of the latter since it was found that this did not significantly affect the relative values of the rate constants of a series of experiments. The rate of the " spontaneous " hydrolysis was redetermined for each separate batch of solvent.

Pyridine (" AnalaR ") was kept over potassium hydroxide for a week and fractionally distilled.

Acetic anhydride (" AnalaR ") was used without purification. Its content of acetic acid was determined by titration of the acid liberated on reaction of a weighed sample of anhydride with aniline.

Rate Measurements.—The hydrolysis was followed by running 10-ml. samples of the reaction mixture, at timed intervals, into aniline. The acid liberated was titrated with carbonate-free alkali (Vles, *Rec. Trav. chim.*, **1933**, **52**, 809). First-order rate constants were evaluated from a graph of log $(T_\infty - T_t)$ against time, where T_t and T_∞ are the titres corresponding to the times t and ∞ respectively (cf. Emery and Gold, *J.*, 1950, 1447). The catalysed reactions did not accurately follow a first-order course, but first-order rate coefficients at the half-life were evaluated from the same graph by evaluating the slope of the nearly linear curve at that point. Such rate coefficients are described by the symbol k_{HL}. The reason for this procedure will appear later. The results are tabulated.

Influence of stoicheiometric pyridine concentration ($[P]_0$) *on rate for different initial concentrations of acetic anhydride* ($[Ac_2O]_0$) at 25·05°.

$[P]_0$ \ $[Ac_2O]_0$	10^4k_{HL} (sec.$^{-1}$)				
	0·038M	0·076M	0·152M	0·303M	0·607M
0	—	—	1·01	—	—
2·43	—	1·39	—	—	—
4·85	2·12	1·79	1·53	—	—
9·71	3·06	2·40	1·89	1·68	—
19·41	—	3·50	2·62	2·11	1·73
38·82	—	—	—	3·24	2·72

Effect of addition of acetic acid on rate of pyridine-catalysed hydrolysis of acetic anhydride at 25·05°.

$[P]_0 = 0{\cdot}00454$M; $[Ac_2O]_0 = 0{\cdot}200$M.

$[AcOH]_0$ (M)	0	0·100	0·200	0·300	0·400	0·600
$[AcOH]_{HL}$ * (M)	0·200	0·300	0·400	0·500	0·600	0·800
10^4k_{HL} (sec.$^{-1}$)	5·39	4·45	3·85	3·51	3·25	2·98

* Concn. of acetic acid in solution after one half-life.

Discussion

Although the kinetics of the catalysed reaction appear superficially complicated, the observations can be explained by elaborating the plausible assumption that the conjugate acid of pyridine is without catalytic activity and that there is a linear catalysis law for the unchanged pyridine. The velocity of the hydrolysis is then given by

$$v = -\frac{d[Ac_2O]}{dt} = [Ac_2O]\left\{k_0 + k_p([P]_0 - [PH^+])\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where k_0 is the velocity coefficient of the " spontaneous " reaction and k_p the catalytic coefficient of pyridine (P). The subscript zero is used to indicate that the concentration term refers to an initial stoicheiometric concentration. It is not necessary for our purposes

to introduce the catalytic coefficients for hydrogen, hydroxide, and acetate ions which do not occur in catalytically significant concentrations.

Application of the law of mass action to the equilibrium

$$P + AcOH \rightleftharpoons PH^+ + OAc^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (A)$$

leads to

$$K = \frac{K_{AcOH} \cdot K_p}{K_w} = \frac{[PH^+][OAc^-]f_{PH^+}f_{OAc^-}}{\{[P]_0 - [PH^+]\}[AcOH]}$$

and hence

$$[PH^+] = \frac{\frac{K}{f_I^2} \cdot [P]_0}{\frac{[OAc^-]}{[AcOH]} + \frac{K}{f_I^2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where K_{AcOH} and K_p are thermodynamic dissociation constants for acetic acid and pyridine, K_w is the ionic product for water, and $f_I^2 = f_{PH^+} f_{OAc^-}$. Activity coefficients for uncharged species have been assumed to be unity. Combining equations (1) and (2), we get

$$v = [Ac_2O]\left\{k_0 + k_p[P]_0\left(1 + \frac{K}{f_I^2} \cdot \frac{[AcOH]}{[OAc^-]}\right)^{-1}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

We may assume that reaction (*A*) does not seriously reduce the concentration of acetic acid molecules in solution after an appreciable amount of hydrolysis has taken place (such as after one half-life) since then $[AcOH] \gg [P]_0$. If it is valid to assume that

$$\frac{K}{f_I^2} \cdot \frac{[AcOH]}{[OAc^-]} \gg 1 \ (i.e., \ [PH^+]/[P] \gg 1) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

we obtain

$$v = [Ac_2O]\left\{k_0 + k_p[P]_0 \frac{f_I^2}{K} \cdot \frac{[OAc^-]}{[AcOH]}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The correctness of assumption (4) cannot be shown rigorously in the absence of measurements of the relevant dissociation constants in aqueous acetone. By analogy with the dependence of dissociation constants on the dielectric constant in dioxan–water (Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," New York, 1950, p. 581; James and Knox, *Trans. Faraday Soc.*, 1950, **46**, 254) we conclude that $K_{AcOH} \sim 10^{-6}$ mole $l.^{-1}$, that $K \sim 1$, and that assumption (4) is probably valid after one half-life of reaction for the experiments with the lowest initial concentration of acetic acid (and, therefore, the lowest concentration of acetic acid at the half-life) and even more so at the higher concentrations.

Since the stoicheiometric concentration of pyridine was always negligible compared with the half-life concentration of acetic acid we may assume that the concentration of acetate ions is entirely governed by the reaction

$$AcOH + H_2O \rightleftharpoons H_3O^+ + OAc^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (B)$$

i.e.,

$$[OAc^-] = [H_3O^+] = \frac{\sqrt{K_{AcOH}[AcOH]}}{f_{II}}$$

where

$$f_{II}^2 = f_{OAc^-} \cdot f_{H_3O^+}$$

Since the degree of ionisation is small we may assume that the concentration of acetic acid molecules in the above equation is equal to the stoicheiometric concentration of acetic acid in the system. Substituting for $[OAc^-]$ in equation (5) we obtain

$$v = [Ac_2O]\{k_0 + R[P]_0[AcOH]^{-\frac{1}{2}}\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

where

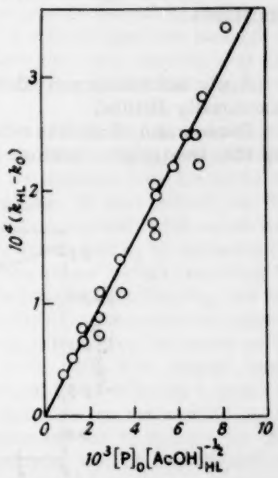
$$R = k_p \cdot \frac{\sqrt{K_{AcOH}}}{K} \cdot \frac{f_I^2}{f_{II}} = k_p \cdot \frac{K_w}{K_p\sqrt{K_{AcOH}}} \cdot \frac{f_I^2}{f_{II}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

In the absence of additional acetic acid, the concentration of acetic acid at the half-life is equal to the initial concentration of anhydride, and therefore the first-order rate coefficient at the half-life (k_{HL}) is given by

$$k_{HL} = k_0 + R[P]_0[Ac_2O]_0^{-\frac{1}{2}} \quad . \quad . \quad . \quad . \quad (8)$$

Equations (6) and (7) only apply at low values of the ratio $[P]_0 : [Ac_2O]_0^{\frac{1}{2}}$ where the assumptions made are least objectionable.

An experimental test of equations (6) and (8) is given in the Figure in which $(k_{HL} - k_0)$ is plotted against $[P]_0[AcOH]_{HL}^{-\frac{1}{2}}$, where $[AcOH]_{HL}$ is the concentration of acetic acid in the system after one half-life. The experimental points represent data for systematic variation of $[Ac_2O]_0$, $[P]_0$, and added acetic acid (see Tables). From the slope, R is found to have the value 0·038 sec.$^{-1}$ (mole l.$^{-1}$)$^{-\frac{1}{2}}$.



Test of equation (6).

By using this value of R in equation (6) it is possible to account quantitatively for the decrease of the first-order rate coefficient during the reaction.

From the rough estimates for K_{AcOH} (1×10^{-6} mole l.$^{-1}$) and K (~1) given, we obtain an approximate value for the catalytic coefficient of pyridine in 50% acetone–water as $k_p \sim 40$ sec.$^{-1}$ mole^{-1} l. Without discussing this result further at this stage we may note that this is an uncommonly large catalytic effect for an uncharged species in any heterolytic reaction in solution. The catalytic constant is approximately 30,000 times greater than that for acetate ions in this solvent, which is remarkable since the acetate ion and pyridine are bases of similar strengths.

King's College, Strand, London, W.C.2. [*Received, January 7th,* 1953.]

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289. *The Hydrolysis of Acetic Anhydride. Part III.* The Catalytic Efficiency of a Series of Tertiary Amines.*

By V. Gold and E. G. Jefferson.

The catalytic effect of a series of heterocyclic tertiary amines on the hydrolysis of acetic anhydride in water at 0° has been studied, and comparative catalytic coefficients have been evaluated for several amines. α-Substituents in the amine decrease the catalytic activity. There was no evidence of formation of an intermediate by interaction of the amine and the anhydride. The experimental facts are consistent with the mechanism proposed, in which the transfer of an acetylium group ($CH_3 \cdot CO^+$) from acetic anhydride to the catalyst is rate-determining, hydrolysis of the resulting cation being rapid. The low frequency factor generally found in bimolecular heterolytic reactions between neutral molecules (of which the uncatalysed acylation reactions are examples) is explained in terms of entropies of solvation. The rôle of amine catalysts in some preparative acylation reactions is briefly discussed.

In view of the remarkable catalysis of the hydrolysis of acetic anhydride by pyridine (Part II *) the effect of other tertiary amines has been examined. The catalytic coefficients were evaluated on the basis of the analysis given in Part II. In order to remove the uncertainties consequent upon the use of a mixed solvent the measurements now reported relate to water at 0° as solvent.

More reliable dissociation constants, at 25°, of several of the amines used have recently been reported (Herington, *Discuss. Faraday Soc.*, 1950, **9**, 26; cf. Gero and Markham, *J. Org.*

* Part II, preceding paper.

Chem., 1951, **16**, 1835) and therefore comparative catalytic coefficients may be deduced from the kinetic data. A slight gap remains in the complete evaluation of catalytic coefficients through lack of knowledge of the temperature dependence of basic dissociation constants.

Experimental

Acetic anhydride was allowed to reflux over magnesium turnings for several days and then fractionally distilled.

Benzoic anhydride was redistilled under reduced pressure and largely freed from benzoic acid by this treatment. Acetone (" AnalaR ") was dried over silica gel and fractionally distilled.

Fig. 1. *Illustration of graphical evaluation of* k_{HL}.

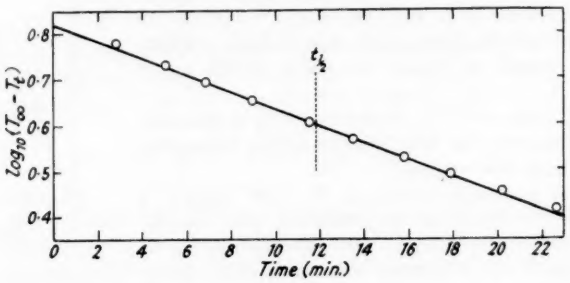
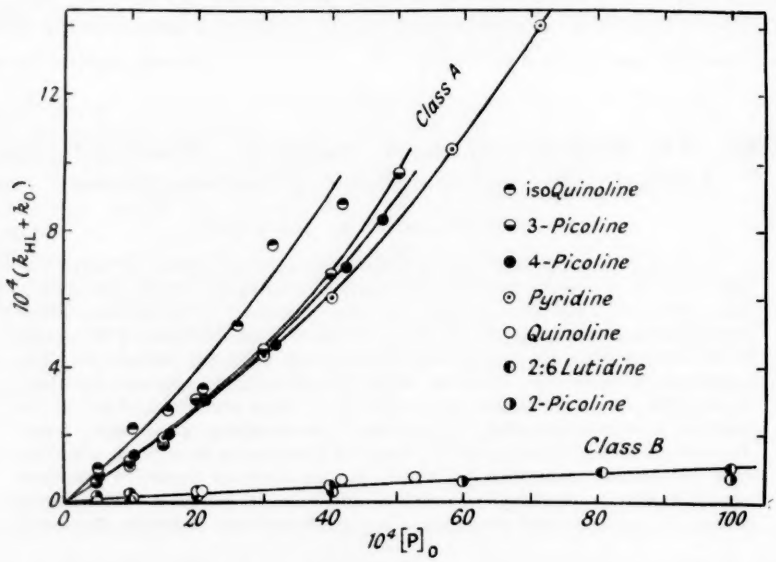


Fig. 2. *Catalytic effect of tertiary amines on the hydrolysis of acetic anhydride.*



For conductivity measurements it was allowed to pass down a column of finely ground silica gel and then fractionally distilled.

Pyridine (" AnalaR ") was purified by the method of Heap, Jones, and Speakman (*J. Amer. Chem. Soc.*, 1921, **43**, 1936), fractionally distilled, and stored over barium oxide.

The picolines (B.D.H.) and 2 : 6-lutidine (Light and Co.) were dried (NaOH) and fractionally distilled. Quinoline (B.D.H.) was also dried over metallic calcium, and *iso*quinoline (Light and Co.) was fractionally frozen. These purification procedures are less stringent than that used for pyridine, and the presence of minor amounts of isomers, homologues, and hydrocarbons

in the purified compounds cannot be ruled out. This possibility cannot, however, introduce an error into our measurements large enough to change the major conclusion.

The procedure for rate measurements and evaluation of rate coefficients was described in Part II. As in the previous experiments, the first-order rate coefficients decreased during the reaction (Fig. 1), and the first-order rate coefficients quoted (k_{HL}) are those after one half-life of reaction. In view of the large heat of hydrolysis of acetic anhydride it was verified that the temperature of the reaction mixture did not differ from that of the thermostat bath by more than 0·01°.

The evaluation of catalytic coefficients was based on equation (6) of Part II. For each catalyst the dependence of k_{HL} on the stoicheiometric concentration of catalyst ($[P]_0$) was studied for a fixed initial concentration of anhydride ($[Ac_2O]_0$). This dependence was found to be linear only at the lowest concentrations of catalyst. Since equation (6) was derived on the assumption that $[P]_0$ is small, the slope of the initial low-concentration portion of the curve was used in the evaluation of R (Fig. 2). R is related to the catalytic coefficient k_p by equation (7) of Part II, and the following assumptions were made regarding the other factors occurring in that equation: (i) The ratio $f_I^2 : f_{II}$ was evaluated from the Debye–Hückel limiting law for activity coefficients; at the ionic strength of 0·05M-acetic acid ($\mu \sim 0{\cdot}001$), this ratio is calculated to have the value 0·96. (ii) The constants K_w and K_{AcOH} are accurately known for water at 0° ($K_w = 1{\cdot}14 \times 10^{-15}$ mole^{-2} l.$^{-2}$; $K_{AcOH} = 1{\cdot}66 \times 10^{-5}$ mole l.$^{-1}$). (iii) The recent basic dissociation constants (*locc. cit.*), at 25°, of some of the amines studied by us differ by a factor of 2—3 from those accepted hitherto. There is, however, no information on the values at 0° or the temperature dependence of the dissociation constants. We preferred not to correct for this temperature variation by some arbitrary procedure based on analogies, but we substituted for K_p in equation (7) the experimental value at 25°. In this way we do not obtain the true catalytic coefficient (k_p) at 0°, but the coefficient k'_p which is related to k_p by the equation $k'_p = k_p(K_p)^0/(K_p)^{25}$, where the superscripts indicate the temperatures to which the dissociation constants refer. For comparisons of the catalytic efficiency of different amines, k'_p is probably almost as useful as k_p since the factor $(K_p)^0/(K_p)^{25}$ would not be expected to depend very markedly on the nature of the amine for the particular series considered.

The conductivity apparatus used has previously been described (Gold, *Trans. Faraday Soc.*, 1948, **44**, 506).

Ultra-violet absorption spectra were measured on a Hilger " Uvispek " Spectrophotometer.

Infra-red absorption measurements were carried out with a Grubb–Parsons single-beam instrument.

The results are tabulated.

TABLE 1. *Rate coefficients for amine-catalysed hydrolyses of acetic anhydride in water at 0°.*

$10^2[Ac_2O]_0$ (M)	$10^4[P]_0$ (M)	10^4k_{HL} (sec.$^{-1}$)	$10^2[Ac_2O]_0$ (M)	$10^4[P]_0$ (M)	10^4k_{HL} (sec.$^{-1}$)	$10^2[Ac_2O]_0$ (M)	$10^4[P]_0$ (M)	10^4k_{HL} (sec.$^{-1}$)
5·01	—	4·48		3-*Picoline*			*Quinoline*	
	Pyridine		5·01	5·0	5·11	4·97	5·2	4·63
			5·20	10·0	5·76	5·02	10·4	4·66
5·03	5·02	5·22	5·45	15·0	6·22	4·96	20·8	4·86
5·10	10·04	5·60	5·34	20·0	7·54	5·05	41·6	5·18
5·08	15·06	6·44	5·35	30·0	9·00	5·11	52·6	5·23
5·06	20·1	7·10	5·35	40·0	11·20			
5·11	30·1	8·81	5·34	50·0	14·2		*iso*Quinoline	
5·09	40·2	10·52				5·10	5·2	5·52
5·36	58·0	14·9		4-Picoline		5·26	10·5	6·70
5·37	71·3	18·5	5·25	5·29	5·28	5·08	15·6	7·21
			5·12	10·6	5·89	5·32	20·9	7·87
	2-*Picoline*		5·21	15·9	6·52	5·19	26·0	9·70
5·06	5·0	4·69	5·09	21·2	7·52	5·22	31·4	12·1
5·08	10·0	4·78	5·26	31·7	8·82	5·31	41·8	13·3
5·01	20·0	4·84	5·31	42·3	11·43			
5·03	40·0	5·01	5·20	47·7	12·80			
5·08	60·0	5·12						
5·03	100·0	5·23		2 : 6-*Lutidine*				
			5·09	5·1	4·57			
			5·10	10·1	4·61			
			4·98	20·2	4·70			
			5·12	40·4	4·84			
			5·07	80·8	5·40			
			5·20	100·1	5·51			

TABLE 2. *Catalytic coefficients for different amines.*

Catalyst	10^3R sec.$^{-1}$ (mole l.$^{-1}$)$^{-\frac{1}{2}}$	$10^{-10}k_p/K_p$ (sec.$^{-1}$)	$10^9(K_p)^{25°}$ (mole l.$^{-1}$)	$10^{-1}k'_p$ (sec.$^{-1}$ mole^{-1} l.)
Pyridine	$28{\cdot}_2$	9·7	1·44 [a]	14
3-Picoline.....	$25{\cdot}_1$	8·6	4·54 [a]	39
4-Picoline	$25{\cdot}_7$	8·8	10·6 [a]	93
*iso*Quinoline	39	13·3	2·5 [b]	33
2-Picoline	$3{\cdot}_4$	1·2	8·77 [a]	11
2 : 6-Lutidine	$2{\cdot}_3$	0·8	38·4 [a]	33
Quinoline	$3{\cdot}_3$	1·1	0·87 [c]	1

[a] Herington, *loc. cit.* [b] Golumbic and Orchin, *J. Amer. Chem. Soc.*, 1950, **72**, 4145. [c] Albert and Goldacre, *Nature*, 1944, **153**, 407.

TABLE 3. *Catalysis of the hydrolysis of benzoic anhydride by pyridine.*

Temp. = 30·02°. Solvent = 50% aqueous acetone (w/w). $[Bz_2O]_0 = 0{\cdot}0221$M.

$10^4[P]_0$ (M)	—	8·68	17·4	34·8
10^6k_{HL} (sec.$^{-1}$)	4·26	8·67	11·1	14·2

DISCUSSION

The amines examined can be divided into two groups according to their catalytic efficiency. At a given stoicheiometric concentration of amine, pyridine, 3- and 4-picoline, and *iso*quinoline (group *A*) are about ten times more effective catalysts than the members of group *B*, made up of 2-picoline, 2 : 6-lutidine and quinoline (cf. values of *R* in Table 2). On evaluation of the catalytic coefficients k'_p this division seems to disappear but it again

TABLE 4. *Test of catalysis law*, $\log k'_p = 10{\cdot}36 + 0{\cdot}92_5 \log K_p$.

Base	$\log K_p$	$\log k'_p$ (calc.)	$\log k'_p$ (expt.)	Difference	Base	$\log K_p$	$\log k'_p$ (calc.)	$\log k'_p$ (expt.)	Difference
Class A.					*Class* B.				
Pyridine ...	$\bar{9}{\cdot}16$	2·18	2·15	−0·03	2-Picoline ...	$\bar{9}{\cdot}94$	2·90	2·04	−0·86
3-Picoline ...	$\bar{9}{\cdot}66$	2·64	2·59	−0·05	2 : 6-Lutidine	$\bar{8}{\cdot}58$	3·50	2·52	−0·98
4-Picoline ...	$\bar{8}{\cdot}03$	2·99	2·97	−0·02	Quinoline ...	$\bar{1}0{\cdot}94$	1·98	1·00	−0·98
*iso*Quinoline	$\bar{9}{\cdot}40$	2·41	2·52	+0·11					

comes into evidence if we attempt to relate the catalytic coefficient to the basic dissociation constant of the amine (Table 4). The members of group *A* follow the Brönsted catalysis law : those of the group *B* appear to have catalytic coefficients only about one-tenth of those to be expected from their basic strengths. The effect may in reality be still more pronounced. It is not impossible (see p. 1411) that some of the feeble catalysis found with amines of group *B* may in fact be due to small amounts of impurities of group *A* amines.

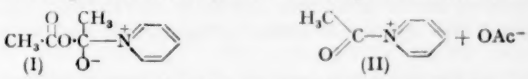
The division into the two groups may be linked with structural similarities. The less active amines are those having a substituent in one or both of the positions adjacent to the heterocyclic nitrogen atom and this suggests steric influence on the mechanism of catalysis. Chemical considerations already render it unlikely that the catalysis involves a proton transfer from anhydride to base, and the steric effect reinforces this view. Furthermore, the hydrolysis of benzoic anhydride (Table 3) is also catalysed by pyridine and in this case the anhydride molecule has no hydrogen atom that could be transferred to the catalyst.

We may also take into consideration the results of related work. It was found that the catalysis is not confined to the acetylation of water, but that pyridine will catalyse the acetylation of *o*-chloroaniline and of ethanol, and that quinoline is again inactive, at least in the former of these reactions (Gold and Jefferson, unpublished work). More significantly still the same division of catalytic amines into two groups occurs in the decomposition of acetic formic anhydride in an aprotic solvent (*idem*, *J.*, 1953, 1416) where the only possible catalytic effect of the amine is by interaction with the anhydride. We therefore suggest that in the hydrolysis too the catalysis is due to an interaction of amine and anhydride, and that it does not take the form of a proton transfer.

Whatever the nature of this interaction, it fairly certainly does not produce an appreciable equilibrium concentration of a new species. All experiments to detect such a product have had negative results : (1) The absorption spectra of pyridine and acetic anhydride in *cyclo*hexane over the range 2300 and 2800 Å (the chief absorption region of pyridine in the

near ultra-violet) are strictly additive. (2) In the infra-red absorption spectra of acetic anhydride and an equimolecular mixture of acetic anhydride and pyridine in carbon tetrachloride the intensity and position of the bands due to carbonyl vibrations (at 1769 and 1936 cm.$^{-1}$) and C–O–C skeletal vibrations (at 1124 cm.$^{-1}$) of acetic anhydride are unaffected by the presence of pyridine. (3) The electrical conductivities of mixtures of acetic anhydride and pyridine in dry acetone were not significantly higher than the sum of the conductivities of solutions of acetic anhydride and of pyridine in acetone; the same result was obtained with benzoic anhydride and pyridine in 50% acetone–water at 0°, *i.e.*, under conditions where the hydrolysis is sufficiently slow to permit reliable back-extrapolation of the conductivity measurements to zero time, but otherwise in a solvent and with an anhydride for which the operation of catalysis has been established. (4) Depressions of the freezing point of benzene by acetic anhydride and pyridine are additive. Thus neither an association complex nor an ionic reaction product between an anhydride and pyridine are formed in analytically detectable amounts.

The view that the catalysis occurs *via* some association between amine and the whole or part of the anhydride molecule is strengthened by the known steric hindrance of α-substituents on the rate and equilibria of association reactions of tertiary amines. The Menschutkin reactions of alkyl chlorides (Long, *J.*, 1911, 2164) and benzyl bromide (Baker and Nathan, *J.*, 1935, 519) with heterocyclic amines proceed more slowly if the amine contains a blocked α-position. The complex of 2-picoline with trimethylboron is much less stable than the analogous complexes of pyridine or 3- and 4-picoline (Brown and Barbaras, *J. Amer. Chem. Soc.*, 1947, **69**, 1137) but more stable than the doubly substituted amine 2 : 6-lutidine; and similarly the complex of boron trifluoride with 2 : 6-lutidine is less stable than that with pyridine (Brown, Schlesinger, and Cordon, *ibid.*, 1942, **64**, 325). There are two chemically plausible interaction products between acetic anhydride and pyridine, *viz.*, (I) and (II) (the formulæ being the classical ones to represent molecules in which the real electron distribution will be such as to minimise the energy), but postulation of the complex (I) does not seem sufficient to explain all the observed catalytic effects. It is difficult to see why the bimolecular reaction of (I) with a water or amine molecule should be easier than that of acetic anhydride alone, and it is even less obvious why a structure such as (I) should be an intermediate in the decomposition of acetic formic anhydride (cf. Ingold, *Trans. Faraday Soc.*, 1941, **37**, 718). If we wish to attribute the higher reactivity of (I) than of acetic anhydride to a greater ease of unimolecular heterolysis, then we are in effect postulating the formation of (II) from (I). A consistent interpretation of the phenomena can be based on the postulate that (II) is the complex between amine and anhydride whose formation is important



(I) (II)

in the catalysis. A structure to which the approximate formula (I) can be assigned would, of course, be the transition state in the formation of (II) from acetic anhydride and pyridine. It does not seem very important for our present purposes to decide whether—with a certain set of equilibrium internuclear distances—a structure (I) also corresponds to a minimum in the potential energy profile, *i.e.*, whether it is a reaction intermediate.

The reaction scheme of the hydrolysis may then be formulated

$$Ac_2O + P \underset{-1}{\overset{1}{\rightleftharpoons}} PAc^+ (II) + OAc^-$$

$$PAc^+ + H_2O \xrightarrow[2]{} AcOH + PH^+$$

where steps 1 and 2 may also be composite (involving the transient formation of free acetylium cations), without experimentally significant consequences. Since no detectable amounts of intermediates are formed we may apply the stationary-state hypothesis,

$$v = -\frac{d[Ac_2O]}{dt} = \frac{\kappa_1\kappa_2[Ac_2O][P]}{\kappa_{-1}[OAc^-] + \kappa_2}$$

where the κ's are the rate coefficients of the individual steps of the scheme. Since the concentration of the reagent water is large and invariant, κ_2 is defined to incorporate the

function of the concentration of water upon which the velocity of this step depends. If we may set

$$\kappa_2 \gg \kappa_{-1}[\mathrm{OAc}^-] \text{ or } \kappa_2 \ll \kappa_{-1}[\mathrm{OAc}]^-$$

simplified forms of this equation are obtained, *viz.*,

$$v = \kappa_1[\mathrm{Ac_2O}][\mathrm{P}]$$

i.e., a rate-determining acetylium-ion transfer from acetic anhydride to pyridine, or

$$v = \frac{\kappa_1\kappa_2}{\kappa_{-1}} \cdot \frac{[\mathrm{Ac_2O}][\mathrm{P}]}{[\mathrm{OAc}^-]}$$

which implies the establishment of a rapid pre-equilibrium made up of reactions 1 and -1. The second simplified equation is not in agreement with experimental facts. The effect of added acetate ion (as sodium or potassium acetate) on the hydrolysis velocity in 50% acetone–water is quantitatively consistent with the assumption that its functions are (*a*) to exert the known catalytic influence of its own, and (*b*) to affect the equilibrium $\mathrm{P} + \mathrm{AcOH} \rightleftharpoons \mathrm{PH}^+ + \mathrm{OAc}^-$ by a mass-law effect. There is no indication that the apparent catalytic coefficient bears an inverse relation to the concentration of acetate ion. The catalysis is therefore thought to operate through the rate-determining heterolysis of the acetic anhydride molecule in a reaction closely analogous to a Menschutkin reaction, followed by rapid attack of water on the cation formed. It is intelligible that, in the absence of steric hindrance, the rate of the slow step should be related to the basic dissociation constant of the amine (Table 4).

The activation energy for the unimolecular heterolysis of acetic anhydride appears to be too unfavourable for such a mechanism to operate in the absence of catalyst. On the other hand, the considerable resonance energy to be expected for PAc^+ allows the rate of this step to become comparable with the bimolecular hydrolysis. The amount of resonance energy is reduced by α-substitution which prevents coplanarity of the C=O bond and the aromatic ring of PAc^+. This inhibition of resonance may be responsible for the strict steric requirements for catalytic efficiency in the amine.

It might be thought that hydrolysis of PAc^+ should still only proceed at a speed comparable to that of hydrolysis of acetic anhydride itself since the two molecules are combinations of acetylium cations with bases of almost identical strength (acetate ion and pyridine). The postulated higher reactivity of PAc^+ is ascribed to a more favourable entropy of activation. The hydrolysis of PAc^+ does not involve a change in the total electrical charge of the reagents and would not require significant reorientation of the solvation shell, whereas the bimolecular hydrolysis of acetic anhydride involves an electrical-charge separation (cf. Gold, *loc. cit.*) requiring the creation of order in the solvent and hence a low entropy of activation.

On this argument an unfavourable entropy of activation would generally be expected for bimolecular heterolytic reactions between unchanged molecules since these must involve highly dipolar transition states and proceed to form two ionic primary reaction products of opposite charges. (These primary products may quickly lose their charges, *e.g.*, by proton transfers involving the solvent.) It is indeed generally found that bimolecular heterolytic reactions between neutral molecules are "slow" reactions (Moelwyn-Hughes, "The Kinetics of Reactions in Solution," Oxford, 1947, 2nd edn., p. 73), *i.e.*, they are characterised by low frequency factors.

It may at first sight appear strange that unimolecular ionisation reactions, such as the ionisation of alkyl halides, do not have such low frequency factors although here too a pair of opposite ionic charges is generated. This apparent inconsistency may be resolved by the following considerations. In the bimolecular reactions considered the charges are generated at positions which are some distance apart and therefore each of them can independently function as a focus for the orientation of solvent molecules. In the unimolecular ionisations, on the other hand, the charge separation in the transition state barely exceeds the equilibrium length of the severed bond and the sphere of influence of the two charges generated will largely overlap. At distances of the order of magnitude of the distance of closest approach of the solvent dipoles the two opposing orientation effects will already largely nullify

each other, and consequently the degree of solvent orientation induced by the formation of the transition state will be less than for the generation of well separated charges. This argument is based on the same physical picture which underlies the theory of the solvent influence on energies of activation (Glasstone, Laidler, and Eyring, " The Theory of Rate Processes," New York, 1941, chapter VIII; cf. Gripenberg, Hughes, and Ingold, *Nature*, 1948, **161**, 480).

The mechanism of the catalysis proposed is specific to the tertiary amines although certain anions may effect catalysis in a similar way. The catalytic action of hydroxide ions (if this term may be used) may again be pictured as being an acetylium-ion transfer analogous to the first step of the pyridine catalysis, *viz.*,

$$Ac_2O + OH^- \longrightarrow AcOH + OAc^-$$

but this first step now constitutes the complete hydrolysis. It has not as yet been established by kinetic measurements whether hydroxide ions will catalyse the acylation of amines and alcohols. It they do—as preparative rules would lead one to suppose—then it seems likely that this catalysis is of a different type and probably involves a proton transfer from the molecule undergoing acylation, *i.e.*,

$$ROH + OH^- \rightleftarrows RO^- + H_2O$$
$$RO^- + Ac_2O \longrightarrow ROAc + OAc^-$$

The catalysis of the hydrolysis by acetate ions can also not be explained on the same lines as the amine catalysis since acetylium-ion transfer to the acetate ion

$$Ac_2O + OAc^- \longrightarrow OAc^- + Ac_2O$$

does not produce a net chemical change. However, since the catalysis by acetate ions is several thousand times weaker than that by pyridine, in spite of the similar basic dissociation constants of the catalysts, it seems reasonable that an explanation along different lines should be sought in this case.

It has sometimes been reported that the use of quinoline as solvent is favourable to acylation reactions and, in some cases, preferable to pyridine. In view of our conclusion that quinoline is a much poorer catalyst, if it is one at all, in the cases we have examined, we tentatively infer that the advantages of quinoline may be (*a*) its high boiling point (which permits heating of the reaction mixture to a high temperature) and (*b*) the presence of catalytically active impurities.

It has been shown (Searles and Cvejanovich, *J. Amer. Chem. Soc.*, 1950, **72**, 3200) that 2-substituted pyridines are much less active than other cyclic amines in catalysing the formation of α-acylamino-ketones from α-amino-acids and acetic anhydride, sometimes known as the Dakin–West reaction (*J. Biol. Chem.*, 1928, **78**, 91, 745). It was suggested by these authors that the function of the tertiary amine was abstraction of a proton from one of the intermediates and that this abstraction was sterically unfavourable in the case of 2-substituted pyridines, although steric hindrance is not usually thought to play such an important rôle in proton-transfer reactions. The observations in the Dakin–West reaction seem analogous to the catalytic effects discovered by us for acylation reactions. While we have no experimental results to disprove the explanation given, we suggest that catalysis of the Dakin–West reaction may be at least equally plausibly attributed to catalysis of one or both of the acylation reactions which seem to make up two of the steps of its mechanism.

Some of the preliminary measurements for this investigation were performed by Dr. S. L. Bafna, whom we thank for his co-operation. We are also indebted to Dr. W. C. Price for allowing us the use of the infra-red spectrometer and his helpful advice. This work has been supported through the award of a maintenance allowance (to E. G. J.) by the D.S.I.R., and through grants towards the cost of apparatus and chemicals from the Royal Society and the Chemical Society respectively.

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290. *Quantitative Studies of the Reactivities of Mixed Carboxylic Anhydrides. Part IV.* The Hydrolysis and Decomposition of Acetic Formic Anhydride.*

By V. Gold and E. G. Jefferson.

The hydrolysis of acetic formic anhydride in acetone–water and its decomposition into acetic acid and carbon monoxide in toluene have been studied kinetically. The hydrolysis is over 100 times faster than that of acetic anhydride in the same medium, in agreement with the principles previously established concerning the effect of structure on the reactivity of mixed carboxylic anhydrides (Part III). The hydrolysis is catalysed by pyridine. The decomposition of acetic formic anhydride is catalysed by heterocyclic tertiary amines, the order of their activity being the same as that for the catalysed hydrolysis of acetic anhydride. The mechanism of the reactions is discussed.

Acetic formic anhydride was first reported and studied by Béhal (*Compt. rend.*, 1899, **128**, 1460; *Ann. Chim. Phys.*, 1900, **20**, 417) who found that it acted as formylating agent towards alcohols and ammonia. It has recently been shown that reaction with aniline (Hurd and Roe, *J. Amer. Chem. Soc.*, 1939, **61**, 3355) and with nitro-alcohols (Hurd, Drake, and Fancher, *ibid.*, 1946, **68**, 789) under mild conditions also leads to the exclusive formation of formyl derivatives. At elevated temperatures (above 50—60°), or in the presence of sulphuric acid, acetyl derivatives are obtained but it seems possible that reaction under these conditions involves decomposition of the mixed anhydride. The formation, under normal conditions, of formyl rather than acetyl derivatives is in accord with the analysis of the factors governing the acylation product ratio given in connection with the study of mixed anhydrides of acetic acid and chloro-aliphatic acids, according to which electronic and steric effects play rôles of comparable importance (Part III *). This analysis has more recently been shown to predict correctly the acylating action of mixed anhydrides of *N*-substituted amino-acids with aliphatic acids (Vaughan and Osato, *ibid.*, 1951, **73**, 5553). In the case of acetic formic anhydride the electronic and steric effects should reinforce each other in favouring formylation relative to acetylation, as is indeed found. The above principles also predict that acetic formic anhydride should be more reactive towards water, amines, and alcohols. This is now confirmed experimentally for the hydrolysis. Acetic formic anhydride is found to hydrolyse over 100 times more rapidly than acetic anhydride in 80% acetone–water. In a dilatometric study of the effects of salts of aliphatic acids on the rate of hydrolysis of acetic anhydride Kilpatrick (*ibid.*, 1928, **50**, 2891) discovered an abnormally large positive catalysis by formate ions and suggested that this was due to the intermediate formation of acetic formic anhydride. Our observation on the reactivity of this substance towards water are not compatible with this hypothesis.

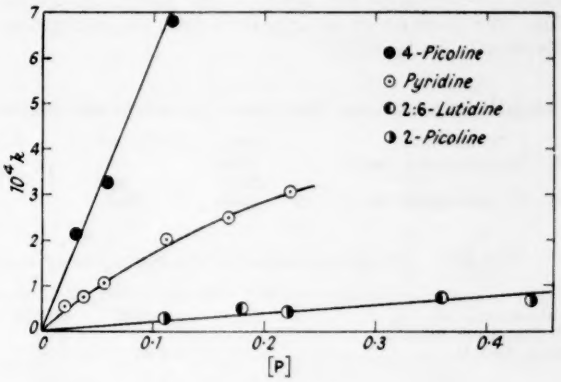
Mixed anhydrides of formic acid are in a special position with regard to the disproportionation reaction (formation of the two symmetrical anhydrides from a mixed anhydride). Since the anhydride of formic acid—if it exists under any feasible conditions—is not stable by itself or in solution at room temperature, the disproportionation is not detectable as such but instead carbon monoxide is formed. A study of this reaction seemed relevant to the elucidation of the problems discussed in the preceding paper. Several qualitative observations are on record that some of the amines which we have found to be catalytically active for acylation reactions of acetic anhydride will also catalyse this decomposition. This seems to be a catalysed reaction of an acid anhydride which does not involve another reagent molecule and indirectly supports the hypothesis that the operation of catalysis in acylation by anhydrides is concerned with action on the anhydride rather than on the water or amine molecule being acylated. However, the observations in the literature (Béhal, *loc. cit.*; Schierz, *J. Amer. Chem. Soc.*, 1923, **45**, 455) are slightly contradictory and

* Part III, *J.*, 1950, 1455.

altogether insufficient to assess the extent of the suspected parallelism between the catalyses in the two reactions.

The results now reported demonstrate that—within the experimental limits—the order of efficiency of pyridine and its homologues in catalysing the decomposition of acetic formic anhydride (see Figure and Table 3) is also the order for the catalysis of the hydrolysis of acetic anhydride. This sequence of catalytic efficiencies differs from the order of the basic dissociation constants of the amines or from the sequence of their catalytic efficiencies for reactions initiated by a rate-determining proton transfer from the substrate to the catalyst (such as the decomposition of nitramide). It has been suggested (preceding paper) that the catalytic efficiency of the amines in the hydrolysis reaction is markedly affected by the steric requirements of a reaction of the catalyst molecule. In view of the close similarity of the results for the hydrolysis and the decomposition it seems reasonable to infer that the catalytic action is similar in the two cases and that it consists in an association between the amine and the whole or part of an anhydride molecule.

The formation of symmetrical formic anhydride, or its catalysed decomposition, is unlikely to be a slow step in the reaction scheme, since the reaction would then have to



Catalytic effect of tertiary amines on the decomposition of acetic formic anhydride.

follow second-order kinetics with respect to anhydride. The range of initial concentration of anhydride over which the reaction has been studied is not extensive but the experiments give no indication of a reaction order greater than unity with respect to acetic formic anhydride. The simplest mechanism in accord with these observations is closely analogous to that suggested for the catalysed hydrolysis of acetic anhydride, involving a rate-determining acylium-group transfer from anhydride to base followed by breakdown of the complex formed :

$$CH_3{\cdot}CO{\cdot}O{\cdot}CHO + P \longrightarrow [P{\cdot}CHO]^+ + OAc^- \longrightarrow PH^+ + CO + OAc^-$$

The second reaction in this scheme may be the unimolecular decomposition of $[P{\cdot}CHO]^+$ or involve more complicated steps. However, the reaction order requires that these cannot be kinetically significant.

The absence of detectable formation of carbon monoxide during the catalysed hydrolysis of acetic formic anhydride indicates that, in 80% acetone–water, the reaction of the complex with water is much more rapid than its decomposition.

Experimental

Acetic formic anhydride was prepared by passing excess of keten into pure formic acid (100 g.) at $\sim -10°$ (Hurd and Roe, *loc. cit.*). The product was twice fractionated under reduced pressure, and 41 g. of a middle fraction (b. p. 25·5—26·5°/10 mm.) were collected for kinetic experiments and stored at a temperature of 0°. The following determinations were carried

out: (1) the acid produced on complete hydrolysis; (2) the acid produced on reaction with dry aniline at 0°; (3) the volume of carbon monoxide evolved on catalysed decomposition with pyridine. From these analyses it was found that the product was 95—96% pure, the most likely impurity remaining after careful fractionation being acetic acid.

The catalytic amines were the specimens used in the work of the preceding paper. "AnalaR" toluene was used as solvent without further purification.

The purification and preparation of the other solvents and reagents have been described in the preceding paper.

Hydrolysis velocities were determined chemically by adaptation of the method previously described (Emery and Gold, *J.*, 1950, 1447; Bafna and Gold, *J.*, 1953, 1406). The uncatalysed hydrolyses strictly obeyed a first-order law. First-order rate coefficients for the catalysed reactions varied with time, and the values quoted refer to the rate after one half-life of reaction. Evolution of carbon monoxide was not observed in any of these experiments.

The velocity of the catalysed decomposition was determined by measuring the rate of evolution of carbon monoxide from the solution. The anhydride was weighed into a solution of the catalyst which was contained in a cylindrical Pyrex vessel (100 ml.). The vessel was vigorously shaken at a constant rate throughout the reaction and was connected to a nitrometer in which the volume of liberated carbon monoxide was measured. For the more rapid decompositions the anhydride was added to the solvent in a sealed capsule which was broken by shaking after isolation of the apparatus from the atmosphere.

The results are tabulated.

TABLE 1. *Spontaneous hydrolysis of acetic formic anhydride.* $[\text{Anhydride}]_0$ ~0·06M.

Solvent	Temp.	10^4k_1 (sec.$^{-1}$)	E (kcal.)	Frequency factor (sec.$^{-1}$)
80% Acetone–water (w/w) ...	0·00°	1·91	10·8	$8·1 \times 10^4$
	20·01	7·52		
50% Acetone–water (w/w) ...	0·00	38·7		

TABLE 2. *Pyridine catalysis of the hydrolysis of acetic formic anhydride.*

Temp. = 0·00°. Solvent = 80% acetone–water (w/w)

$[\text{Anhydride}]_0$ (M)	0·0607	0·0601	0·0606	0·0611	0·0603
10^3 [Pyridine] (M)	—	1·66	3·32	5·38	8·50
10^4k_{HL} (sec.$^{-1}$)	1·91	5·41	8·60	11·7	14·3

TABLE 3. *Rate coefficients for the catalysed decomposition of acetic formic anhydride in toluene at 39·92°.*

10^2 $[\text{Anhydride}]_0$ (M)	$10^2[\text{P}]_0$ (M)	10^3k (sec.$^{-1}$)	10^2 $[\text{Anhydride}]_0$ (M)	$10^2[\text{P}]_0$ (M)	10^3k (sec.$^{-1}$)	10^2 $[\text{Anhydride}]_0$ (M)	$10^2[\text{P}]_0$ (M)	10^3k (sec.$^{-1}$)
~5	—	I.s.*	P = 4-*Picoline*			P = 2-*Picoline*		
P = *Pyridine*			4·50	2·87	21·5	4·51	11·02	2·90
4·62	2·21	5·56	4·31	5·74	32·8	4·62	22·04	4·28
5·21	3·69	7·60	4·23	11·47	68·3	4·70	44·07	6·56
6·04	5·53	10·6	4·22	22·94	137			
5·98	11·07	20·2	4·46	45·37	223	P = 2 : 6-*Lutidine*		
4·51	16·59	24·9				4·73	18·01	5·01
6·43	22·13	30·5				4·63	36·03	7·31

* Imperceptibly slow.

We thank the D.S.I.R. for a maintenance allowance (to E. G. J.).

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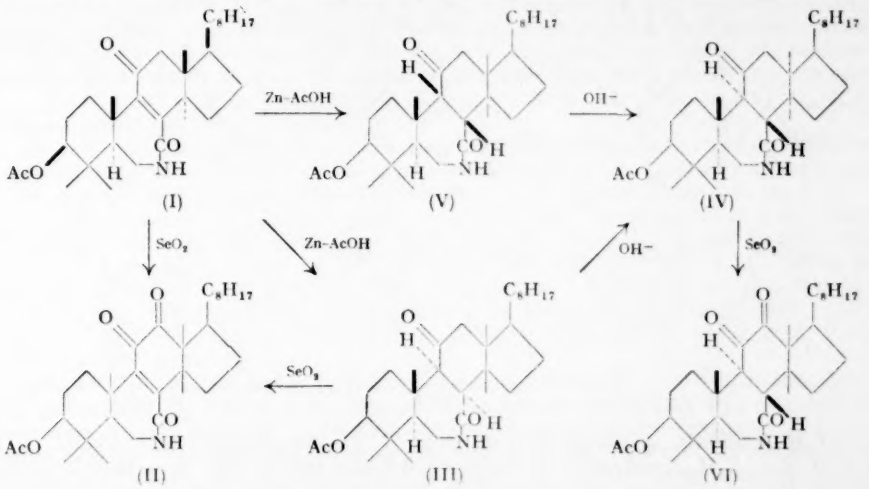
291. *Triterpenoids. Part XI.* Some Stereospecific Reactions in the Lanostadienol (Lanosterol) Series.*

By C. S. Barnes and D. H. R. Barton.

Reduction of 7 : 11-diketo-6*a*-aza-B-homolanost-8-en-3β-yl acetate† by zinc dust and acetic acid affords both 8α : 9α- and 8β : 9β-7 : 11-diketo-6*a*-aza-B-homolanostan-3β-yl acetate. Both compounds are isomerised by alkali, to give, after re-acetylation, the corresponding 8β : 9α-isomer. The course of selenium dioxide oxidation of these and related compounds leads to the generalisation that ready conversion of ane-1 : 4-diones into ene-1 : 4-diones requires a *cis*-relation for the eliminated hydrogen atoms.

In Part VII of this series (Barnes, Barton, Fawcett, and Thomas, *J.*, 1952, **2339**; see also Falco, Voser, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 2430) there is described the preparation of a number of nitrogenous derivatives of lanostadienol. In continuation of this work several observations of stereochemical interest have been made.

Oxidation of 7 : 11-diketo-6*a*-aza-B-homolanost-8-en-3β-yl acetate† (I) with selenium dioxide gives the triketone (II) (Barnes *et al.*, *loc. cit.*), whereas reduction with zinc dust and acetic acid affords a saturated keto-amide, m. p. 184—185°. This is readily converted into (II) on selenium dioxide oxidation. The stereochemistry of this keto-amide is now regarded as 8α : 9α (III) on the basis of the following evidence. The zinc–acetic acid re-



duction of (I) also affords in minor amount a stereoisomeric amide, m. p. 284—286°. Both this amide and (III) are isomerised by methanolic potassium hydroxide to give, after re-acetylation, a further stereoisomer, m. p. 274—276°, which is the most stable of the four possible stereoisomers. Accordingly we formulate the isomer of m. p. 274—276° as the 8β : 9α-compound (IV) with a complete *trans-anti-trans* arrangement of asymmetric centres (cf. W. S. Johnson, *Experientia*, 1951, **7**, 315; *J. Amer. Chem. Soc.*, in the press).

Now whereas (III) is only isomerised slowly to (IV), the amide of m. p. 284—286° isomerises very rapidly (see Experimental section). It is logical therefore to regard the latter process as isomerisation at the α-position to the keto-group, and the former as isomerisation at the α'-position to the amide function. On this basis the stereochemistry of

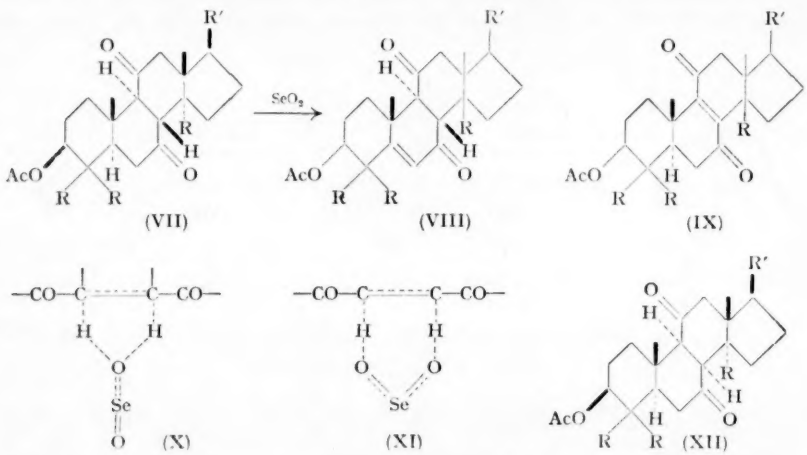
* Part X, *J.*, 1953, 576.

† We have now adopted steroid numbering for lanostadienol and its derivatives (cf. forthcoming paper by E. R. H. Jones, T. G. Halsall, and their collaborators). The adoption of steroid numbering also has the approval of Dr. J. F. McGhie.

(III) follows, and the amide, m. p. 284—286°, must be the 9-β-compound (V). The formation of the two amides (III) and (V) involves *cis*-addition of hydrogen. Such a stereochemical course for the reduction of ene-1 : 4-diones has already been exemplified (Barton, Holness, Overton, and Rosenfelder, *J.*, 1952, 3751) and may even be the normal mode of reduction, although frequently obscured by subsequent isomerisation to the more stable *trans*-form.

When the amide (IV) was subjected to selenium dioxide oxidation it gave in good yield 7 : 11 : 12-triketo-6*a*-aza-B-homolanostan-3β-yl acetate (VI). This reaction is in marked contrast with the course of the selenium dioxide oxidation of (III) (see above), where the double bond is readily reintroduced between $C_{(8)}$ and $C_{(9)}$. These observations, coupled with other considerations outlined below, lead us to the conclusion that the ready selenium dioxide oxidation of the system $-CO\cdot\underset{|}{C}H\cdot\underset{|}{C}H\cdot CO-$ is a stereospecific process in which the hydrogen atoms should be *cis* to each other.

Apart from the above-mentioned example, there are at least two other cases where the *trans*-stereochemistry of the hydrogen atoms of an ane-1 : 4-dione makes difficult selenium dioxide oxidation to an ene-1 : 4-dione. 7 : 11-Diketolanostanyl acetate (VII; R = Me, R′ = C_8H_{17}) gives 7 : 11-diketolanost-5-enyl acetate (VIII; R = Me, R′ = C_8H_{17}) (Dorée, McGhie, and Kurzer, *J.*, 1949, 570) and *not* 7 : 11-diketolanost-8-enyl acetate (IX; R = Me, R′ = C_8H_{17}). Similarly we have found that 7 : 11-diketoergostanyl acetate (VII; R = H,



R′ = C_9H_{19}) affords, although in poor yield, 7 : 11-diketoergost-5-enyl acetate (VIII; R = H, R′ = C_9H_{19}), and *not* 7 : 11-diketoergost-8-enyl acetate (IX; R = H, R′ = C_9H_{19}). Barton, Holness, Overton, and Rosenfelder (*loc. cit.*) showed that whereas methyl 12 : 19-diketo-18α-oleananolate acetate was resistant to selenium dioxide oxidation, the stereoisomeric 18β-compound was readily oxidised. Such a difference in reactivity is in consonance with the present generalisation, for the 18α-compound has the $C_{(13)}$ and $C_{(18)}$ hydrogen atoms *trans*, and the 18β-compound has the *cis*-arrangement at these centres.

So far as the mechanism of the selenium dioxide oxidation is concerned the present results indicate that a molecular reaction with a cyclic transition state [(X) or (XI) or an equivalent] may be involved.

After the completion of our investigations as outlined above, Professor F. S. Spring, F.R.S., very kindly informed us of his preparation (with Budziarek; see *J.*, 1953, 956) of 7 : 11-diketo-8α-ergost-22-enyl acetate (XII; R = H, R′ = C_9H_{17}) by modified zinc dust reduction of 22 : 23-dibromo-8α : 9α-epoxy-7 : 11-diketoergostan-3β-yl acetate and related compounds. With Professor Spring's kind permission we have confirmed the reduction to (XII; R = H, R′ = C_9H_{17}) and have shown that, as expected, selenium dioxide oxidation (in ethanol solution) of the latter gives in excellent yield 7 : 11-diketo-

ergosta-8 : 22-dien-3β-yl acetate (IX; R = H, R′ = C_9H_{17}) with preferential *cis*-elimination of hydrogen. Under the same conditions 7 : 11-diketoergostan-3β-yl acetate was not attacked; it was even recovered unchanged after 24 hr. refluxing with an excess of selenium dioxide in ethanol.

Experimental

Unless specified to the contrary, rotations were determined in chloroform at room temperature and light-absorption maxima in ethanol.

For general experimental see Part VII (*J.*, 1952, 2339). Infra-red spectra were kindly determined by Dr. J. E. Page (of Glaxo Laboratories Ltd.) in carbon disulphide solution using a Perkin–Elmer double-beam instrument.

Reduction of 7 : 11-*Diketo*-6a-*aza*-B-*homolanost*-8-*en*-3β-*yl Acetate* (I).—The unsaturated amide (4 g.) was refluxed in " AnalaR " acetic acid (100 ml.), and zinc dust (5 g.) added during 1 hr. Chromatography over alumina (ether–benzene mixtures) afforded the 7 : 11-diketo-6*a*-aza-B-homo-8α-lanostan-3β-yl acetate (III) (3·5 g.), m. p. 184—185°, described in Part VII (*J.*, 1952, 2339). Crystallisation of the last (ether) eluted fractions from methanol afforded 7 : 11-*diketo*-6a-*aza*-B-*homo*-9β-*lanostan*-3β-*yl acetate* (V), m. p. 284—286°, $[\alpha]_D$ +70° (*c*, 1·07) (Found : C, 74·6; H, 10·15; N, 2·5. $C_{32}H_{53}O_4N$ requires C, 74·5; H, 10·35; N, 2·7%).

Alkaline Isomerisation of 7 : 11-*Diketo*-6a-*aza*-B-*homo*-8α- *and* -9β-*lanostan*-3β-*yl Acetate*.—The 8α-keto-amide (III) (600 mg.) in 10% methanolic potassium hydroxide was refluxed for 5 hr. The product was acetylated (pyridine–acetic anhydride at 100° for 30 min.). Recrystallisation from chloroform–methanol gave 7 : 11-*diketo*-6a-*aza*-B-*homolanostan*-3β-*yl acetate* (IV), m. p. 274—276°, $[\alpha]_D$ +4° (*c*, 2·20), +23° (*c*, 0·51 in MeOH; 2-dm. tube), $\lambda_{max.}$ 300 mμ (ε 60) (Found : C, 74·8; H, 10·3; N, 2·7. $C_{32}H_{53}O_4N$ requires C, 74·5; H, 10·35; N, 2·7%). Alkaline hydrolysis of the 9-β-keto-amide (V) followed by reacetylation gave the same product.

The 7 : 11-keto-amide acetate (IV) (100 mg.) was hydrolysed by refluxing 5% methanolic potassium hydroxide for 15 min. Crystallisation from benzene gave the *alcohol*, m. p. 138—145°, $[\alpha]_D$ −25° (*c*, 1·15), −15° (*c*, 1·03 in MeOH) (Found : C, 75·75; H, 10·65; N, 2·6. $C_{30}H_{51}O_3N$ requires C, 76·05; H, 10·85; N, 2·95%).

The rates of isomerisation of the above mentioned keto-amides were also determined on a more quantitative basis as follows. Methanolic potassium hydroxide (10·0 ml.; 5%) was added to the appropriate keto-amide (100 mg.), and the mixture rapidly brought to the b. p. At suitable time intervals (*t*, min.) the reaction was stopped by rapid cooling and the rotation determined. The following results were obtained : (III); *t* = 0, $[\alpha]_D$ +118° (*c*, 0·49; 2-dm. tube); *t* = 2, +100° (*c*, 1·00); *t* = 60, +97°; *t* = 180, +60°; *t* = 300, +50°; [using 10% potassium hydroxide *t* = 2, +99° (*c*, 1·00); *t* = 15, +82°; *t* = 180, +14°; *t* = 300, +7°, *t* = 600, −9°]. (V); *t* = 0, $[\alpha]_D$ +95° (*c*, 0·11; 4-dm. tube); *t* = 5, +11° (*c*, 1·00); *t* = 25, −10°; *t* = 60, −10°. (IV); *t* = 0, +20° (*c*, 0·54; 2-dm. tube); *t* = 15, −9° (*c*, 1·00); *t* = 60, −11°; *t* = 300, −11°.

Selenium Dioxide Oxidation of 7 : 11-*Diketo*-6a-*aza*-B-*homo*-8α-*lanostan*-3β-*yl Acetate* (III).—The keto-amide (III) (100 mg.) was refluxed with selenium dioxide (150 mg.) in " AnalaR " acetic acid (10 ml.) for 3 hr. After crystallisation from chloroform–methanol, the product was identified as 7 : 11 : 12-triketo-6*a*-aza-B-homolanost-8-en-3β-yl acetate (II) (Barnes, Barton, Fawcett, and Thomas, Part VII, *loc. cit.*) by m. p., mixed m. p., rotation, and absorption spectrum.

Selenium Dioxide Oxidation of 7 : 11-*Diketo*-6a-*aza*-B-*homolanostan*-3β-*yl Acetate* (IV).—The keto-amide (IV) (100 mg.) was refluxed with selenium dioxide (200 mg.) in " AnalaR " acetic acid for 2 hr. Crystallisation from chloroform–methanol gave 7 : 11 : 12-*triketo*-6a-*aza*-B-*homolanostan*-3β-*yl acetate* (VI), m. p. 262—263°, $[\alpha]_D$ −9° (*c*, 0·60), $\lambda_{inflex.}$ *ca.* 320 mμ (ε 85), $\lambda_{max.}$ 430 mμ (ε 75) (Found : C, 72·5; H, 9·7; N, 2·4. $C_{32}H_{51}O_5N$ requires C, 72·55; H, 9·7; N, 2·65%). It gave no colour with ferric chloride. On chromatography in benzene solution over alumina this compound (1·0 g.) afforded 7 : 12-*diketo*-11-*hydroxy*-6a-*aza*-B-*homolanost*-9(11)-*en*-3β-*yl acetate* (720 mg.). Recrystallised from chloroform–methanol this had m. p. 274—276°, $[\alpha]_D$ −63° (*c*, 1·08), $\lambda_{max.}$ 283 mμ (ε 9000) (Found : C, 72·6; H, 9·55; N, 2·75. $C_{32}H_{51}O_5N$ requires C, 72·55; H, 9·7; N, 2·65%). It gave an immediate intense ferric chloride reaction.

Hydrogenation of 7 : 11-*Diketoergost*-22-*en*-3β-*yl Acetate*.—The ane-dione (5 g.) was hydrogenated over platinum in ethyl acetate (700 ml.) and 60% perchloric acid (2 drops) (cf. Hershberg, Oliveto, Rubin, Staeudle, and Kuhlen, *J. Amer. Chem. Soc.*, 1951, **73**, 1144). After reoxidation with chromium trioxide in acetic acid, the 7 : 11-*diketoergostan*-3β-*yl acetate* (VII;

R = H, R′ = C_9H_{19}), crystallised from methanol, had m. p. 194—195°, $[\alpha]_D$ −12° (*c*, 1·20), $\lambda_{max.}$ 300 mμ (ε 70) (Found: C, 75·7; H, 10·05. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·25%).

Selenium Dioxide Oxidation of 7 : 11-*Diketoergostan-3β-yl Acetate*.—The ane-dione (VII; R = H, R′ = C_9H_{19}) (2 g.) was refluxed with selenium dioxide (1·5 g.) in acetic acid for 3 hr. The product was chromatographed from benzene over neutralised alumina. Crystallisation from light petroleum (b. p. 60—80°) gave 7 : 11-*diketoergost-5-en-3β-yl acetate* (VIII; R = H, R′ = C_9H_{19}), m. p. 183—185°, $[\alpha]_D$ −48° (*c*, 0·97), $\lambda_{max.}$ 234 mμ (ε 10,500) (Found: C, 76·75; H, 10·05. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%). In the infra-red the compound showed carbonyl bands at 1735 and 1235 (acetate), 1710 (saturated ketone in six-membered ring), and 1678 cm.$^{-1}$ (αβ-unsaturated ketone in six-membered ring).

Selenium Dioxide Oxidation of 7 : 11-*Diketo-8α-ergost-22-en-3β-yl Acetate* (XII; R = H, R′ = C_9H_{17}).—The ane-dione (150 mg.), prepared from 22 : 23-dibromo-8α : 9α-epoxy-7 : 11-diketoergostan-3β-yl acetate (Budziarek, Johnson, and Spring, *J.*, 1952, 3410) by the method of Budziarek and Spring (*loc. cit.*), was refluxed with selenium dioxide (100 mg.) in absolute ethanol (25 ml.) for 30 min. The precipitated selenium was filtered off and the product crystallised from chloroform–methanol, to give 7 : 11-diketoergosta-8 : 22-dien-3β-yl acetate, m. p. 136—138°, $[\alpha]_D$ +26° (*c*, 0·90), $\lambda_{max.}$ 270 mμ, (ε 9500) (cf. Heusser, Eichenberger, Kurath, Dällenbach, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2107; Chamberlin, Ruyle, Erickson, Chemerda, Aliminosa, Erickson, Sita, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 2396).

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BIRKBECK COLLEGE, LONDON, W.C.1. [*Received, January* 14*th*, 1953.]

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292. *The Enzymic Synthesis and Degradation of Starch. Part XVIII.* The Minimum Chain-length for Q-Enzyme Action.*

By STANLEY PEAT, W. J. WHELAN, and J. M. BAILEY.

The minimum length of an unbranched amylose-type chain which functions as substrate for Q-enzyme has been determined by two methods. It is shown that the minimum length for *rapid* transglucosidation by Q-enzyme is about 40 glucose units. A slow branching action is observed when Q-enzyme acts upon substrates of shorter chain-length. Thus, a synthetic, linear, 28-unit dextrin was branched at a much slower rate than was a 58-unit dextrin.

THE plant enzyme (Q-enzyme) responsible for the synthesis of the ramified polysaccharide amylopectin is a transglucosidase (see Parts VII and XII, *J.*, 1950, 93; 1951, 596). The initial substrate for this action consists of unbranched amylose-type chains, and a proportion of the α-1 : 4-links of these chains are converted into α-1 : 6-links by the transferring action. The length of the linear chains must exceed a certain determinable minimum if the rate of branching is to be comparable with that occurring with natural amylose, the chain-length of which is *ca.* 1000 units. It was shown in Part XII (*loc. cit.*) that this minimum length was greater than 25 units since α-dextrins (from amylose) having this average length were unattacked by Q-enzyme within the normal period of completed action on amylose. This is the same molecular size as was originally postulated for "pseudo-amylose" (Part I, *J.*, 1945, 877) which was considered to be an intermediate in amylopectin synthesis. The present work is concerned with a precise determination of the minimum length of linear chain which can serve as substrate for rapid Q-enzyme action. Since the publication of our preliminary account (*Biochem. J.*, 1952, **51**, xxxiv), Nussenbaum and Hassid have reported that potato Q-enzyme is without action on linear dextrins of average chain-lengths 23, 30, and 42 glucose units, but converts a 116-unit dextrin into amylopectin (*J. Biol. Chem.*, 1952, **196**, 785).

* Part XVII, *J.*, 1952, 722.

As a preliminary to this work an investigation was made to define the pattern of action of potato phosphorylase and it was proved that the synthesis of amylose induced by this enzyme proceeds by the apposition of glucose residues (from glucose-1 phosphate) simultaneously to all the primer molecules (Bailey and Whelan, *Biochem. J.*, **1952**, **51**, xxxiii). The successful separation and purification of suitable primers, the maltodextrins (Bailey, Whelan, and Peat, *J.*, **1950**, **3692**), thus made possible the enzymic synthesis of linear molecules of accurately known chain-length which could serve as substrates for Q-enzyme action.

One method of approach was to prepare a series of linear amylose-type molecules of known chain-length and to test each individually for susceptibility to Q-enzyme action. Alternatively, by incorporating Q-enzyme in a digest in which synthesis by phosphorylase was proceeding and comparing the course of reaction with that effected by phosphorylase acting alone, the onset of Q-enzyme action could be readily determined; the average chain-length of the substrate molecule at that point is calculated from a knowledge of the initial molar concentration of primer and the amount of phosphate liberated from the glucose-1 phosphate. The detection of Q-enzyme activity makes use of the facts that the branched product of its action has a lower intensity of iodine stain and a lower degree of β-amylolysis than has the linear substrate.

The results of experiments of the second type are shown by Fig. 1 which correlates the intensity of iodine stain (at 680 mμ) and the degree of polymerisation (equivalent to chain

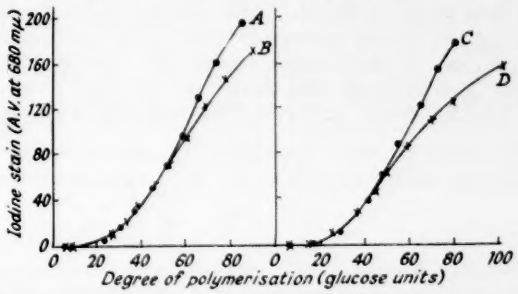


FIG. 1. *Synthesis of polysaccharides by* (1) *phosphorylase* (*curves A and C*) *and* (2) *phosphorylase and Q-enzyme* (*curves B and D*).

length in the case of unbranched polysaccharides) of polysaccharides synthesised (i) by phosphorylase and Q-enzyme acting together (curve *B*) and (ii) by phosphorylase alone (curve *A*). It will be seen that the two curves are coincident until the degree of polymerisation is greater then 49 glucose units, at which point Q-enzyme begins to synthesise branched products exhibiting a lower intensity of iodine stain than do the linear products of phosphorylase synthesis. Obviously the value, 49, represents the minimum chain-length of a linear substrate on which the branching action of Q-enzyme is detectable in this experiment. The light-absorption curves of the iodine-stained polysaccharides also confirmed that the onset of Q-enzyme action was marked by a lowering of $\lambda_{max.}$ relative to that observed in the absence of Q-enzyme. It should be reiterated that in the presence of Q-enzyme, measurements of " chain-length " beyond this point have no real significance since Q-enzyme operates against the chain-lengthening action of phosphorylase by its branching action. The numerical results of this experiment might well have depended on the relative amounts of the two enzymes present, since in the presence of an excess of phosphorylase, Q-enzyme action might not become detectable until the chain-length of the synthetic linear substrate had been appreciably increased beyond the minimum. In a second similar experiment, the ratio of Q-enzyme to phosphorylase was increased five-fold and the results confirmed the above conjecture since the apparent minimum length of chain susceptible to rapid attack by Q-enzyme was lower, namely 42 units (Fig. 1, curves *C* and *D*). Experimental difficulties prevented a higher enzyme ratio from being employed but the alternative means, described below, of following Q-enzyme action provided a more accurate estimate of this minimum chain-length for rapid branching activity. At intervals during the second experiment portions were removed from both digests, the enzymes were

inactivated by heat, and β-amylase was added. After 10 minutes' incubation the new digests were stained with iodine. The results (Fig. 2) indicated that at no stage during synthesis by phosphorylase acting alone did any iodine-staining β-dextrin remain after the subsequent action of β-amylase. When both phosphorylase and Q-enzyme were present, however, the β-amylolysis was incomplete (as indicated by the presence of iodine-staining β-dextrin) if the degree of polymerisation (calculated) of the initial linear product was greater than 40 units.

These results indicate that the minimum chain-length for *rapid* Q-enzyme action is about 40 glucose units. This does not preclude the possibility that the enzyme may exert

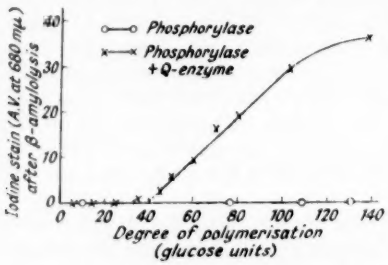
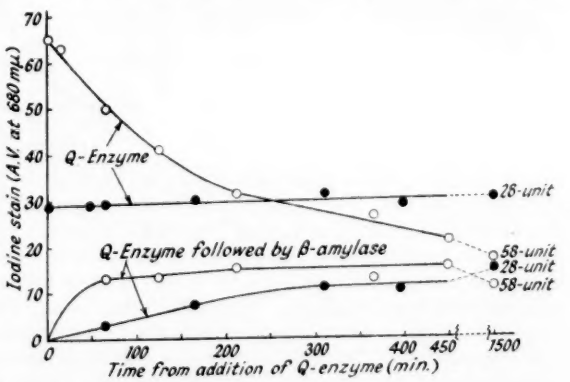


FIG. 2. *Branching by Q-enzyme.*

a slow action on shorter chains, and in fact the figure of 40 units must be an approximation since the factors governing synthesis by phosphorylase dictate that an appreciable distribution of chain-length around the average must always exist and become wider as synthesis proceeds even though the action of phosphorylase follows, as already stated, the "simultaneous" pattern. Thus with chains averaging 40 units in length the distribution,

FIG. 3. *Action of Q-enzyme on 28-unit and 58-unit synthetic maltodextrins.*



within practical limits, is of the order of ±10 units (Dr. A. W. Boyne, personal communication).

In a third approach two amylose-dextrins of average length 28 and 58 units respectively were synthesised by phosphorylase action and, after deactivation of the phosphorylase, Q-enzyme was allowed to act on the individual polysaccharides. Fig. 3 shows the progress of each reaction with respect to changes in (i) the intensity of iodine stain of the products of Q-action and (ii) the extent of production of β-limit dextrin by the successive actions of Q-enzyme and β-amylase, also measured by the iodine-staining method. With respect to the changes under (i), it will be seen that, although Q-enzyme effected a steady diminution in the intensity of stain of the 58-unit substrate, no change in that of the 28-unit dextrin took place. The latter observation would, in terms of all previous experience, have suggested that Q-enzyme had no action on the 28-unit dextrin. Nevertheless when portions of the digests were subjected to β-amylolysis it was obvious, from the persistence of β-limit dextrins, that Q-enzyme was, in fact, utilising the 28-unit as well as the 58-unit dextrin.

In a similar experiment, a comparison of the relative rates of action of Q-enzyme on the two linear polysaccharides, in terms of the initial rates of formation of β-limit dextrin (measured by iodine-staining) when Q-enzyme and β-amylase were allowed to act successively, showed that the 58-unit dextrin was branched by Q-enzyme 25 times as fast as the 28-unit dextrin. This is an indication that what appears to be the minimum chain-length value (40 units) is really the substrate length at which Q-enzyme action becomes sufficiently rapid to be perceptible under the given conditions.

A more precise formulation of the action-pattern of Q-enzyme may now be envisaged. Two possibilities have been considered. In type (i), two chain molecules take part, a " donor " chain, in which an α-1 : 4-linkage is severed, and an " acceptor " chain. A glucose member of the acceptor chain provides a primary hydroxyl group for the formation of an α-1 : 6-linkage with the reducing group liberated from the " donor " chain. Type (ii) requires only one chain and involves three stages : first, the scission of an α-1 : 4-link ; secondly, the movement of the severed portion along the remainder of the original chain ; and finally the establishment of an α-1 : 6-linkage between the two chain fragments. The following evidence may be cited in favour of the first mechanism. It has been shown that substances which are not, in the usual sense, substrates for Q-enzyme action may take part in the reaction. This was demonstrated for the Q-enzyme of *Polytomella coeca* by Barker, Bebbington, and Bourne (*Nature*, 1951, **168**, 834) who found that the addition of amylopectin, glycogen, dextrins, or even maltose to a digest of amylose and this Q-enzyme increased the rate of reaction. Rees and Hanes (unpublished experiments with the Q-enzyme of potato) have observed that maltodextrins appear to be incorporated in the synthetic polysaccharide if they are incubated with a mixture of the enzyme and amylose. These experiments make clear that a distinction must be drawn between the linear substrate (the " donor "), the length of which, as we have shown, must be at least 40 glucose units for rapid Q-enzyme action, and the " acceptor " molecule, the characteristics of which are differently defined, since maltose will fulfil this rôle. Obviously any molecule which can act as a donor in this sense will also function as an acceptor, but it does not follow that the reverse proposition is true.

Experimental

Analytical Methods.—(*a*) *Determination of inorganic phosphate.* Allen's method (*Biochem. J.*, 1940, **34**, 858) was used in a modified form because it was found that when inorganic phosphate was determined in presence of glucose-1 phosphate appreciable hydrolysis of the latter occurred within the period of development of the colour. This hydrolysis was almost completely eliminated by the use of 1 ml. instead of 2 ml. of " Amidol " reagent in a final volume of 25 ml., the other reagents, namely perchloric acid and ammonium molybdate, being used in the prescribed amounts. In consequence of this change the sensitivity of the method was lower by 8%. When a Spekker photometer, Ilford 608 filters, and 1-cm. cells were used, 0·1 mg. phosphorus ≡ 0·635 scale reading, the mean deviation being ±0·001. The possibility that the digest components used in polysaccharide synthesis might interfere with the determination of phosphate was tested as follows. The free phosphate in a solution of potassium phosphate (P, 0·1 mg./ml.) was estimated by the modified Allen procedure with and without the addition of a boiled digest containing potato phosphorylase, glucose-1 phosphate, maltohexaose (primer), ammonium molybdate, and mercuric chloride. The results of the experiment, given in the Table, show that the digest components did not interfere with the determination of phosphate.

Phosphate solution (ml.) :	0	0·1	0·3	0·4	0·5
	Colour intensity (" Eel " colorimeter units)				
I. Phosphate solution	0	9·9	29·7	39·7	49·5
II. Phosphate solution +0·2 ml. of digest	14·0	23·4	44·0	53·7	63·8
III. (II) less 14·0	0	9·4	30·0	39·7	49·8

(*b*) *Measurement of iodine stain.* The synthetic polysaccharides were stained with a 0·2% solution of iodine in 2% potassium iodide. The light absorption at 680 mμ [A.V. (680 mμ)] was measured with the " Eel " colorimeter, and light-absorption curves with the Unicam spectrophotometer.

Preparation of Enzymes.—(a) *Phosphorylase and Q-enzyme.* The use of iron-containing vessels and apparatus was avoided and the ammonium sulphate solution was freed from iron

by heating it to 70—80°, adjusting it to pH 10 with ammonia (*d* 0·880), stirring in 1 g. of silica/l., and filtering the mixture through a Seitz filter. The pH was readjusted to 7·0 with sulphuric acid, and the salt concentration to 50 g./100 ml. The juice of Kerr's Pink potatoes was used to prepare a lead complex eluate (Part IV, *J.*, 1949, 1705) which was fractionated as follows. For phosphorylase the protein precipitated at between 19 g. and 35 g. of ammonium sulphate per 100 ml. was collected, dissolved in 100 ml. of water, and reprecipitated twice, the 19—35 g. and 22—35 g. fractions being collected successively. The final precipitate was dissolved in 0·2M-citrate buffer (20 ml.; pH 7·0), then centrifuged, and the solution freeze-dried. The yield (from 500 ml. of juice) was 5 g. and the activity 28 units/g. (Green and Stumpf, *J. Biol. Chem.*, 1942, **142**, 355). Q-Enzyme was precipitated from the lead eluate at an ammonium sulphate concentration of 19 g./100 ml., redissolved in 100 ml. of water, centrifuged, and reprecipitated at the same salt concentration. After dissolution in citrate buffer (50 ml.) the solution was freeze-dried, yielding 4·8 g. of powder from 560 ml. of juice.

(b) β-Amylase was prepared from soya beans as in Part XV (*J.*, 1952, 705).

Polysaccharide Synthesis in Presence and Absence of Q-Enzyme.—(a) *Low* Q/P *ratio.* Two digests were prepared containing maltohexaose primer (0·575 ml.; 2·3 mg.; prepared as in *J.*, 1953, 1293, 0·1M-glucose-1 phosphate (4 ml.; pH 7·0), 8% ammonium molybdate (0·5 ml.; see Bailey *et al.*, *Biochem. J.*, 1951, **49**, lvi), 0·2M-citrate buffer (5 ml.; pH 7·0), and phosphorylase (1 ml.; 75 mg.). The second digest contained also Q-enzyme (1 ml.; 100 mg.), and the volume of each digest was adjusted to 25 ml. with water. The phosphorylase was added last, and immediately after dilution a portion of each digest (1 ml.) was used in determination of the initial inorganic phosphate content, the enzymes being inactivated by the perchloric acid used in this determination. Prior removal of the enzyme protein by trichloroacetic acid precipitation was found to be unnecessary; the coloured solutions were very slightly turbid but a precipitate was not formed. The digests were incubated at 35° and measurements of inorganic phosphate were made at intervals by using progressively smaller aliquots. The average chain-length (in glucose units) of the polysaccharide synthesized at each stage was calculated from (i) the inorganic phosphate liberated and hence the molar amount of glucose-1 phosphate decomposed and (ii) the molar concentration of the primer, maltohexaose. Portions (0·5 ml. each) of the digests were also removed and stained with iodine solution (0·5 ml.) in a total volume of 25 ml., containing 1 drop of 6N-sulphuric acid. The experimental results are plotted in Fig. 1 (curves *A* and *B*).

(b) *High* Q/P *ratio.* Two digests were prepared, identical in composition with those given above except in respect of enzyme concentration. The first contained phosphorylase (1 ml.; 40 mg.), and the second, phosphorylase (0·85 ml.; 34 mg.) and Q-enzyme (1 ml.; 250 mg.). The smaller amount of phosphorylase in the second digest was to compensate for the slight phosphorylase activity of the Q-enzyme preparation, the correction being necessitated by the high Q/P ratio. The course of polysaccharide synthesis was followed as in the first experiment and, in addition, portions (1 ml. each) were incorporated in digests containing 0·2M-acetate buffer (1 ml.; pH 3·6), purified soya-bean β-amylase (0·05 ml.; 200 units), and water (3 ml.). Under these conditions phosphorylase and Q-enzyme activities were entirely suppressed and a control experiment showed that β-amylolysis of the synthetic polysaccharide was complete within 6·5 min. The digests were incubated for 15 min. at room temperature; then iodine (0·5 ml.), 6N-sulphuric acid (1 drop), and water (to 10 ml.) were added. The A.V. (680 mμ) was then measured with the "Eel" colorimeter. The results of the above experiments are plotted in Figs. 1 and 2.

Synthesis of Amyloses of Known Chain-length.—A digest was prepared containing maltohexaose primer (6·9 ml.; 27·6 mg.), 0·1M-glucose-1 phosphate (30 ml.; pH 7·0), 0·2M-citrate buffer (5 ml.; pH 7·0), 8% ammonium molybdate (3 ml.), potato phosphorylase (110 mg.), and water (to 100 ml.). The digest was incubated at 35° and portions (0·3 ml.) were used in determination of inorganic phosphate. When the calculated chain-length of the synthetic polysaccharide was approx. 30 units a portion (50 ml.) of the digest was withdrawn and the enzyme inactivated by being heated at 100° for 5 min. Determination of the inorganic phosphate content of the cooled solution showed that the polysaccharide chain-length was 28 units. When, in the remainder of the digest, the chain-length had reached approx. 60 units, a second portion (40 ml.) was withdrawn and treated similarly The resulting polysaccharide had an average chain-length of 58 units. Coagulated protein was removed on a Seitz filter. Some retrogradation occurred when the solutions were kept (within 3 hr. for the 58-unit dextrin and overnight with the 28-unit dextrin). The 58-unit polysaccharide was redissolved by treating the solution (30 ml.) with 6N-sodium hydroxide (3 ml.) and heating. The cooled solution was

neutralised with 6N-hydrochloric acid and diluted to 50 ml. with water (solution *A*). The solution (40 ml.) of the 28-unit dextrin was treated similarly (solution *B*).

Action of Q-Enzyme on the Synthetic Amyloses.—Solutions *A* and *B* were incorporated in three digests of the following composition. Each contained Q-enzyme (250 mg.) and 0·2M-citrate buffer (2 ml.; pH 7·0); in addition, digest (1) contained solution *A* (20 ml.); digest (2), solution *A* (10 ml.) + solution *B* (10 ml.); and digest (3), solution *B* (20 ml.). Each digest was diluted to 25 ml. with water and incubated at 21°. Portions [0·5 ml. of digests (1) and (2) and 1 ml. of digest (3)] were withdrawn at intervals and stained with iodine (0·5 ml.) before dilution to 25 ml. with water. The A.V. (680 mμ) of each solution was measured by using the "Eel" colorimeter. At similar intervals, portions (2 ml.) from each digest were incubated for 10 min. at room temperature with purified soya-bean β-amylase (0·01 ml.; 50 units) and 0·2M-acetate buffer (1 ml.; pH 3·6). Portions (1 ml.) were stained with iodine (0·5 ml.) in a final volume of 10 ml., and the A.V. (680 mμ) of each was measured. The results with digests (1) and (3) are plotted in Fig. 3. The relative rates of action of Q-enzyme on the two polysaccharides were more accurately compared by a repetition of the above experiment with two digests, each containing Q-enzyme (50 mg.) and 0·2M-citrate buffer (2 ml.; pH 7·0). The first contained the 28-unit dextrin (9·1 mg.), and the second the same weight of the 58-unit dextrin. The rates of formation of β-dextrin were measured from the tabulated results.

Successive actions of Q-enzyme and β-amylase on synthetic amyloses.

Period of Q-enzyme action (min.)	A.V. (680 mμ) 58-Unit dextrin	28-Unit dextrin
12	3·4	—
28	4·8	0·2
66	7·0	0·7
243	9·9	2·9

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293. *The Electrochemistry of Boron Trifluoride Co-ordination Compounds. Part VII.* Degrees of Ionic Dissociation in the Molten State.*

By N. N. GREENWOOD and R. L. MARTIN.

Evidence is presented which unequivocally establishes that the electrical conductivity of molten boron trifluoride complexes is due entirely to self-ionic dissociation of the co-ordination compounds. The percentage of ions free to conduct in a melt is shown to be numerically equivalent to the reduced conductivity, $\mathfrak{K} = \mu\eta$, provided that the ratio of the activation energies of viscosity and conductivity, $m' = E_\eta/E_\mu$, is unity. This leads to values of the order of 10% for the degree of dissociation of the hydroxyl-containing complexes of boron trifluoride with water, alcohols, and acids, and 0·1% for the complexes with ethers, esters, and tertiary amines. The conduction characteristics of boron trifluoride complexes are compared with those of molten alkylammonium picrates and fused inorganic halides, to emphasize the conditions under which the calculations of the degree of ionic dissociation are valid.

BORON TRIFLUORIDE forms a number of organic and inorganic co-ordination compounds of varied catalytic activity (Booth and D. R. Martin, "Boron Trifluoride and its Derivatives," John Wiley & Sons, New York, 1949; Kästner, "Newer Methods of Preparative Organic Chemistry," Interscience Publ., New York, 1948). Discussions on the mechanism of catalysis in these liquids have, in the past, been largely speculative and often hampered by lack of precise information on the constitution of the molten phase;

* Part VI, *J.*, 1953, 757.

they have often assumed the existence of carbonium and other ions in the molten complex or reaction mixture and it has been the object of the present series of papers to investigate experimentally the hypothesis of ionic dissociation in boron trifluoride co-ordination compounds.

Preceding papers have demonstrated that the boron trifluoride compounds with water (Part IV, *J.*, 1951, 1915), alcohols (Part VI, *J.*, 1953, 757), ether (Part I, *J.*, 1950, 3030), acetic acid (Parts II and III, *J.*, 1951, 1328, 1795), and alkyl acetates (Part V, *J.*, 1953, 751) all conduct electricity. In addition, the electrical conductivities of boron trifluoride complexes with phenol (Sowa, Hinton, and Nieuwland, *J. Amer. Chem. Soc.*, 1933, **55**, 3402), triethylamine (Greenwood, unpublished observations), pyridine (R. L. Martin, unpublished observations), orthophosphoric and pyrophosphoric acids (Topchiev, Paushkin, Vishnyakova, and Kurashov, *Doklady Akad. Nauk. S.S.S.R.*, 1951, **80**, 381) are known (see Table 1).

TABLE 1. *Boron trifluoride co-ordination compounds at* 25°.

Compound	M. p.	$10^4\kappa$ (ohm^{-1} cm.$^{-1}$)	μ (cm.^{2} ohm^{-1})	E_μ (kcal. mole^{-1})	E_η	m'	$\mathfrak{K}$ (cm.^{3} cp. ohm^{-1})	Ref.
BF_3,H_2O	6·0°	245 †	1·17 †	3·7	3·8	1·0	10·5 †	Pt. IV
$BF_3,2H_2O$	6·2	779	4·98	3·2	4·1	1·3	17·2	Pt. IV
BF_3,MeOH ...	−18·6	124	0·883	3·1	3·2	1·0	2·22	Pt. VI
BF_3,2MeOH ...	−58·1	295	3·22	2·6	2·9	1·1	7·34	Pt. VI
BF_3,EtOH ...	−19	85·4	0·718	—	—	—	—	*a*
BF_3,2EtOH ...	—	106	1·46	2·8	2·9	1·0	4·13	*b*
BF_3,2Pr^{n}OH ...	—	38	0·68	4·1	4·1	1·0	3·10	*b*
BF_3,PhOH.....	—	5·28	—	—	—	—	—	*a*
BF_3,2PhOH ...	—	11(50°)	—	—	—	—	—	*c*
BF_3,AcOH ...	37·5	12·5 *	0·108 *	~8·5 *	~9·2 *	1·1	5·06 *	Pt. III
BF_3,MeOAc ...	65·5	6·74(65°)	0·0766	6·4	5·0	0·8	0·175(65°)	Pt. V
BF_3,EtOAc ...	32·5	1·24 *	0·0155 *	7·2 *	6·6 *	0·9	0·090 *	Pt. V
BF_3,Pr^{n}OAc ...	14·7	0·938	0·0133	6·5	7·2	1·1	0·094	Pt. V
BF_3,Bu^{n}OAc ...	17·9	0·319	0·0051	9·1	6·9	0·8	0·039	Pt. V
BF_3,Et_2O	−57·7	2·96	0·0374	3·4	3·1	0·9	0·071	Pt. I
BF_3,Et_3N	29·8	2·45 †	0·042 †	5·0	4·8	1·0	0·34 †	*b*
BF_3,C_5H_5N ...	48·4	5·09(50°)	—	—	—	—	—	*b*
BF_3,H_3PO_4 ...	−105	72·3	0·615	—	—	—	23	*a*
$(BF_3)_2,H_4P_2O_7$	−82	67	1·08	—	—	—	~105	*a*
						Mean 1·0		

* Supercooled liquid. † Extrapolated.

a, Topchiev, Paushkin, Vishnyakova, and Kurashov, *Doklady Akad. Nauk. S.S.S.R.*, 1951, **80**, 381; 1951, **80**, 611. *b*, Greenwood and Martin, unpublished observations. *c*, Sowa, Hinton, and Nieuwland, *J. Amer. Chem. Soc.*, 1933, **55**, 3402.

However, the existence of a measurable conductivity does not necessarily establish that the conducting entities are ions or that such ions are characteristic of the melt. Electrical conductivity may arise in any of the following ways: (i) self-ionic dissociation of the melt (*e.g.*, fused sodium chloride); (ii) ionic dissociation of dissolved impurities (*e.g.*, aqueous electrolytes); (iii) semi-conductivity (*e.g.*, fused lead sulphide); (iv) metallic conductivity (*e.g.*, liquid mercury); (v) various combinations of the preceding four mechanisms. That purified boron trifluoride co-ordination compounds conduct entirely by virtue of their *self-ionic dissociation* is consistent with the following evidence, which also eliminates the other four possibilities. (*a*) The compounds exhibit well-defined decomposition potentials, D, in the molten state (Parts I, II, IV, and VI); this eliminates all but (i), (ii), and (v). The value of D is characteristic for each complex; this renders (ii) and (v) unlikely. (*b*) Faraday's laws of electrolysis have been established (Parts II and IV); this eliminates all except (i) and (ii). (*c*) Electrolysis yields electrode products which are characteristic for each complex and are readily interpreted in terms of its empirical formula (Parts I, II, IV, and VI); this eliminates all except (i) and (v). (*d*) The shape of the conductivity–composition isotherms: reaction between two components of negligible conductivity ($<10^{-10}$—10^{-7} ohm^{-1} cm.$^{-1}$) results in an immediate increase to values in the range 10^{-4}—10^{-1} ohm^{-1} cm.$^{-1}$. Minima in these isotherms correspond with 1 : 1 or 1 : 2 stoicheiometric ratios of the components (Parts II, IV, V, and VI; Sowa, Hinton, and Nieuwland, *loc. cit.*;

Nieuwland, Vogt, and Foohey, *J. Amer. Chem. Soc.*, 1930, **52**, 1018); this eliminates all but (i) and, possibly, (iii). (*e*) The large increase in conductivity on melting (Parts III and IV); this eliminates (iii) and (iv). (*f*) The inverse relation between conductivity and viscosity (Parts I, III, IV, V, and VI); this eliminates (iii) and (iv). In short, electronic mechanisms are excluded by each of the six criteria, and of the two possible ionic mechanisms, (i) and (ii), conduction due to electrolytes present as impurity is eliminated by arguments (*a*), (*c*), and (*d*).

Degree of Ionic Dissociation.—The extent to which the molten complexes are dissociated into ions has not previously been evaluated. In this section, a method of estimating the degree of dissociation, α, is developed and the conditions under which it is reliable are examined. A distinction is drawn between ionization, which implies an appreciable separation of charge within a molecule, and ionic dissociation, which involves the separation of a molecule into anions and cations which are free to migrate under an applied potential. In this paper the extent to which kinetically free ions are formed is estimated: the structure of the undissociated form of the complex is not involved; it may or may not be ionized. In the same way, the mechanism of the dissociation process and the factors which influence the degree to which it occurs are not considered. The calculations merely determine the percentage of molecules which have undergone dissociation into ions in a given system.

The relation $\kappa = nev$ between the specific conductivity (κ), the number (n) of charge carriers, their charge (e), and mobility (v) shows that, if κ and v could be measured, the number of charge carriers and hence the degree (α) of ionic dissociation could be calculated. It is difficult to devise methods for measuring ionic mobilities in pure melts, so that, in the absence of experimental values of v, calculation of α turns on an ability to estimate the mobility satisfactorily. The ensuing discussion is centred on finding valid conditions for estimating v; this done, the degree of dissociation follows without difficulty.

In general, the specific conductivity, κ, and molar conductivity, $\mu = M\kappa d^{-1}$ vary exponentially with temperature:

$$\kappa = \kappa_0 e^{-E_\kappa/RT} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$\mu = \mu_0 e^{-E_\mu/RT} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where M is the molecular weight, d the density, κ_0 and μ_0 are constants, and E_κ and E_μ are activation energies of ionic migration calculated on the basis of 1 ml. and 1 mole of compound, respectively. At room temperature E_κ and E_μ are very similar, differing only by about 0·1 kcal. mole^{-1}, but it has recently been shown that at higher temperatures the difference may be appreciable, and that use of E_μ rather than of E_κ is preferred for comparative purposes (R. L. Martin, to be published).

Frequently, the viscosity may also be represented by an exponential relation,

$$\eta = \eta_0 e^{E_\eta/RT} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where E_η is the activation energy for the process of viscous flow. Elimination of T from equations (1) and (3) gives the relation

$$\kappa^m\eta = \text{constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where $m = E_\eta/E_\kappa$. Similarly, from equations (2) and (3) it follows that

$$\mu^{m'}\eta = \text{constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where $m' = E_\eta/E_\mu$. Values of E_μ, E_η, and m' calculated from the slopes of plots of log μ against $1/T$ and log η against $1/T$ are presented in Table 1 for a number of boron trifluoride complexes.

It is important for the present argument to note that $m' \sim 1$ for all the complexes; its mean value is 1·0. These values should be compared with those given in Table 3 for molten salts where m' is frequently considerably greater than unity.

By inserting $m' = 1$ in equation (5) it is seen that $\mu\eta$ = const., *i.e.*, Walden's rule is experimentally established for boron trifluoride systems. The function $\mu\eta$ has been used by many authors to compare the relative conducting powers of electrolytes, because it is independent of molar concentration (or molar volume) and also makes allowance for

variation of mobilities caused by changes in viscosity. However, it has frequently been overlooked that this linear dependence of mobility on fluidity ($1/\eta$) implies that similar configurational changes occur in ionic migration and viscous flow, as shown by a similarity in the activation energies of the two processes. The function $\mu\eta$ has been termed the "reduced conductivity" (Part III) and is denoted by $\mathfrak{K}$. Reduction of the specific conductivity κ to a standard state of 1 mole and unit viscosity does, in fact, give an almost temperature-independent function (see Parts I and III—VI for experimental results).

In the case of a molten uni-univalent electrolyte the specific conductivity will be given by the formula

$$\kappa = n_+ e v_+ + n_- e v_- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

As the number of cations and anions are equal, this becomes

$$\kappa = ne(v_+ + v_-) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where n is the number of charge carriers of one sign. The number of moles of compound per ml. is dM^{-1} so that the number of molecules is

$$n_0 = NdM^{-1} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

where N is Avogadro's number. From (7) and (8) it follows that the ratio of the number of ions of one sign to the total original number of molecules is

$$\frac{n}{n_0} = \frac{M\kappa}{Nde(v_+ + v_-)} = \frac{M\kappa}{2Ndev} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

where v is now the average mobility of cations and anions in a medium of viscosity η. From the experimental fact established above that $m' = 1$, this mobility may be related to a standard reference mobility v_0 in a medium of unit viscosity (1 cp.) by using the relation

$$v = v_0\eta^{-1} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

In a uni-univalent electrolyte, the number of ions of one sign equals the number of dissociating molecules, so that equations (9) and (10) give the percentage degree of ionic dissociation as

$$\alpha = \frac{n}{n_0} = \frac{M\kappa\eta}{d} \cdot \frac{100}{2Nev_0} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

Values of v_0 are limited to a very narrow range of mobilities. Thus, reference to tables of ionic mobilities in aqueous or non-aqueous solutions (Kortüm and Bockris, "Textbook of Electrochemistry," Elsevier Publ. Co. Inc., 1951, p. 701) indicates that in any particular solvent *all mobilities are within a factor of ten of each other*. In water, for which the viscosity at 20° is 1·00 cp., all ions except hydrogen and hydroxyl have mobilities in the range $2{\cdot}5 \times 10^{-4}$ to 10×10^{-4} cm.^{2} sec.$^{-1}$ volt^{-1}, so that a value $v_0 = 5 \times 10^{-4}$ cm.^{2} sec.$^{-1}$ volt^{-1} represents all mobilities to within a factor of 2. Because of the established relation between mobility and viscosity it is also valid to use this figure as a plausible standard average mobility in boron trifluoride complexes when reduced to unit viscosity. With this figure, the numerical value of the term $100/2Nev_0$ in equation (11) becomes unity, so that the percentage degree of ionic dissociation is given directly by the reduced conductivity:

$$\alpha \sim \mu\eta = \mathfrak{K} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

In this way, the values of $\mathfrak{K}$ listed in Table 1 give a useful indication of the extent to which boron trifluoride complexes dissociate into ions. The compounds with water, alcohols, and acetic acid are 2—20% dissociated into ions. The compounds with ortho- and pyro-phosphoric acid are also highly dissociated, but it is not possible to identify $\mathfrak{K}$ with α here as it has not been established whether the compounds dissociate into uni-univalent or uni-multivalent ions. It will be noted that all these compounds contain a hydroxyl group in the molecule. On the other hand, complexes with ethyl ether and the esters are only weakly dissociated; values of α vary between 0·04 and 0·2%, indicating that their melts are predominantly molecular. These conclusions are consistent with the chemical behaviour of the various complexes.

It is stressed that these are order-of-magnitude calculations only. For this reason too much weight should not be placed on the apparently systematic decrease of α with

increasing chain length of the alcohols and esters. It would be safe to conclude, though, that the acetate complexes are considerably less dissociated than the acetic acid complex. The viscosity correction is not likely to introduce serious error for the reasons discussed earlier, but the arbitrary value of v_0 used for all complexes might introduce some error as it is based on data for infinite dilution. Many of the complexes considered have ionic concentrations of the order of 1 molar and for these more highly dissociated compounds, estimates of α are likely to be low. (The number of moles per litre is $1000dM^{-1}$ of which $\alpha\%$ are ionized; hence there are $10\alpha dM^{-1}$ moles per litre as free ions.)

Comparison with Other Molten Systems.—The conclusions deduced in the preceding section are supported by a re-analysis of the data of Walden, Ulich, and Birr (*Z. physikal. Chem.*, 1927, **130**, 495; 1928, **131**, 1, 21) for 22 molten picrates, with $\mathfrak{K}$ as a basis for estimation of the degree of ionic dissociation. Although these authors did not represent their conductivity and viscosity results in exponential form, their data do, in fact, conform to such equations and, when plotted in this way, lead to the values of E_μ, E_η, and m' given in Table 2. Here again the proximity of m' to unity permits an interpretation of the reduced conductivity in terms of the degree of ionic dissociation.

From Table 2 the average value of $\alpha_{150°}$ for primary alkylammonium picrates is 36% and for secondary alkylammonium picrates, 37%. This is consistent with these authors' conclusions from other arguments (*ibid.*, 1928, **131**, 31; Walden, *ibid.*, 1931, **157**, 389) that primary and secondary alkylammonium picrates are incompletely dissociated.

The behaviour of the tertiary salts showed them to be the weakest electrolytes and this is consistent with the present evaluation of their reduced conductivity which is equivalent to an average degree of dissociation of 12%. The best-conducting picrates were the quaternary ammonium salts and it was concluded that these were practically completely dissociated into ions. The present concepts give a formal value of 48% as the average for salts in this class.

TABLE 2. *Alkylammonium picrates at* 150°.

Compound (Pic = picrate)	M. p.	$10^4\kappa$ (ohm^{-1} cm.$^{-1}$)	μ (cm.^{2} ohm^{-1})	E_μ (kcal. mole^{-1})	E_η (kcal. mole^{-1})	m'	$\mathfrak{K}$ (cm.^{3} cp. ohm^{-1})
Et·NH_3Pic	169·8°	80 *	1·67 *	7·6	7·9	1·0	~45 *
Pr^n·NH_3Pic	144	61·1	1·31	9·6	11·7	1·2	40·6
Bu^n·NH_3Pic	150·3*d*	50·3	1·16	9·7	10·3	1·1	33·0
Bu^i·NH_3Pic	150·3*d*	48·2	1·11	9·8	12·0	1·2	41·1
n-C_5H_{11}·NH_3Pic	143·5	42·5	1·07	10·1	11·8	1·2	31·4
iso-C_5H_{11}·NH_3Pic	132·8	35·6	0·888	11·3	12·5	1·1	33·4
n-C_7H_{15}·NH_3Pic	124·2	30·1	0·864	10·7	11·8	1·1	25·7
Me_2NH_2Pic	160—161	19 *	3·75 *	6·0	8·4	1·4	~60 *
MeEtNH_2Pic	96·8	156·3	3·36	7·4	8·7	1·2	47·4
Et_2NH_2Pic	70·7	131·5	3·12	6·9	6·9	1·0	29·7
$Pr^n_2NH_2$Pic	98·6	91·2	2·48	7·7	7·7	1·0	29·1
$(n\text{-}C_5H_{11})_2NH_2$Pic	94·5	40	1·39	8·7	9·2	1·1	19·3
Et_3NHPic	174·5	70 *	1·88 *	7·9	7·4	0·9	~20 *
Pr^n_3NHPic	114—115	41·4	1·35	9·0	7·4	0·8	10·3
$(iso\text{-}C_5H_{11})_3$NHPic	124·6	12·4	0·546	9·8	8·9	0·9	5·1
$Me_2Pr^n_2$NPic	93	176·5	5·36	7·0	8·1	1·2	48·4
Et_3Pr^nNPic	144·2	165·1	5·23	6·9	6·7	1·0	50·1
$Et_2Pr^n_2$NPic	79·8	171·5	5·66	6·8	7·6	1·1	48·0
$MePr^n_3$NPic	82·2	156·7	5·29	7·2	7·8	1·1	46·2
$EtPr^n_3$NPic	107·2	151·1	5·33	7·4	7·9	1·1	45·9
Pr^n_4NPic	119·6	139·8	5·19	7·2	7·9	1·1	45·2
$(iso\text{-}C_5H_{11})_4$NPic	87·0	59·6	3·10	7·1	9·5	1·3	47·0
					Mean	1·1	

* Extrapolated. *d* = with decomp.

Instructive comparisons may also be drawn from the field of high-melting inorganic salts. Table 3 presents a representative selection of the data available on these salts, recalculated where necessary to evaluate the quantities required by the present analysis. It will be noted that values of $\mathfrak{K}$ lie between 141 for molten potassium bromide and 361 for molten silver iodide and it might be thought that this argues against the identification of the reduced conductivity with the degree of ionic dissociation as developed above.

These molten salts, however, in contradistinction to the systems with boron trifluoride and the picrates, do not fulfil the essential condition that m' equals unity. In such melts, where m' is very different from unity, there is little justification for assuming that use of the reduced conductivity $\mathfrak{K}$ (*i.e.*, $\mu\eta$) effects an adequate viscosity correction [cf. equation (5)]. In fact, the disparity between E_η and E_μ is a clear indication that in these melts different structural processes are involved in viscous flow on the one hand and ionic migration on the other. This is frequently (Bloom and Heymann, *Proc. Roy. Soc.*, 1947, *A*, **188**, 392; Frenkel, " Kinetic Theory of Liquids," Clarendon Press, Oxford, 1946) taken to indicate that, whereas viscous flow involves a breakdown of the configuration of both anions and cations and will depend mainly on the resistance to shear of the larger ions (usually the anions), electrical conductance will be primarily determined by the freedom of movement of the smaller ions (usually the cations) through the interstices between the larger ions. This is reflected, for example, in the distinct increase in E_μ and corresponding decrease in μ which is observed on passing from lithium chloride to cæsium chloride, whilst E_η remains approximately constant. Similarly the conductivity of silicate melts is increased by addition of metal oxides, the greatest increase being produced by oxides of univalent metals with small cationic radii (Bockris, Kitchener, Ignatowicz, and Tomlinson, *Trans. Faraday Soc.*, 1952, **48**, 75).

Despite the large values of m' in many inorganic melts, which arise from the differences between E_η and E_μ, it is possible to effect a partial correction for the influence of viscosity on mobility. This results from the general relation that, when both molar conductivity and viscosity vary exponentially [equations (2) and (3)], they must themselves be connected by equation (5), *viz.*, $\mu^{m'}\eta = \text{const.}$ or $\mu\eta^{1/m'} = \text{const.}$ This suggests that, in the general case, reduction of conductivities to a standard state of unit viscosity should be made by using $\eta^{1/m'}$ rather than η itself. The derivation leading to equation (12) would then give the percentage of ionic dissociation as $\alpha \approx \mu\eta^{1/m'}$. Values of this function are listed in Table 3. The value of $\mu\eta = 141$ for potassium bromide now reduces to $\mu\eta^{1/m'} = 109$, and the value of $\mu\eta = 361$ for silver iodide becomes $\mu\eta^{1/m'} = 121$. These calculations, therefore, confirm that the particular molten salts in Table 3 are completely ionized, yielding numerical values as close to 100% as may be expected in view of the approximations involved.

TABLE 3. *Molten inorganic halides at their m. p.**

Compound	M. p.	κ (ohm^{-1} cm.$^{-1}$)	μ (cm.^{2} ohm^{-1})	E_μ (kcal. mole^{-1})	E_η (kcal. mole^{-1})	m'	$\mathfrak{K}$ (cm.^{2} cp. ohm^{-1})	$\mu\eta^{1/m'}$
NaCl	800°	3·54	134	2·70	9·4	3·5	196	149
KCl	768	2·12	104	3·26	7·8	2·4	157	123
NaBr	740	2·93	129	2·58	10·6	4·1	185	141
KBr	728	1·61	90	3·42	7·9	2·3	141	109
AgCl	455	3·77	112	1·20	5·3	4·4	333	143
AgBr	422	2·75	92	0·99	~5·0	5·1	348	119
AgI	552	2·36	99	0·90	5·8	6·4	361	121
					Mean	4·0		

* Data from Biltz and Klemm (*Z. anorg. Chem.*, 1926, **152**, 267), Ward (*Trans. Faraday Soc.*, 1937, **33**, 88), and Bloom and Heymann (*Proc. Roy. Soc.*, 1947, *A*, **188**, 392). In some instances the m. p. is appreciably below the accepted value.

A comprehensive review of data is not the present purpose. However, the general methods developed in this paper have been found to apply with equal success to the many compounds for which specific conductivity, viscosity, and density are known over a range of temperature and for which it has been established that conduction is due to an ionic transport mechanism.

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294. *The Oxidation of Monoethenoid Fatty Acids and Esters. The Preparation and Catalytic Oxidation of Highly Purified Brassidic Acid by Gaseous Oxygen.*

By J. H. Skellon and C. G. Taylor.

Modified processes are detailed for the preparation of highly purified brassidic acid, from the fatty acids of rape oil, by making use of urea complexes.

A study of the changes occurring during, and of the oxidation products of, the catalytic oxidation of brassidic acid by gaseous oxygen at 120° and 73° with uranyl brassidate as catalyst has shown that there is little rupture of the carbon chain, the main products being dihydroxybehenic acid and an oily monomeric complex containing keto-hydroxy- or keto-unsaturated derivatives. Brassidic acid hydroperoxide is more stable than that of erucic acid, at moderate temperature, and the *trans*-acid is again generally less susceptible to oxidation than the *cis*-isomer. The results of high-temperature oxidation have confirmed existing views on the mechanism of oxidation of monoethenoid fatty acids.

The object of the present investigation was to compare the course of catalytic autoxidation of brassidic acid (*trans*-docos-13-enoic acid) with that of the *cis*-isomer (Skellon and P. E. Taylor, *J.*, 1952, 1813; Dorée and Pepper, *J.*, 1942, 477), and elaidic acid (*trans*-octadec-9-enoic acid) (Skellon and Thruston, *J.*, 1949, 1626, 1953, 138). Brassidic acid was obtained by isomerisation of purified erucic acid, prepared by adaptation of Schlenk and Holman's procedure (*J. Amer. Chem. Soc.*, 1950, **72**, 5001) for the separation of urea complexes of the fatty acids. This method is superior to the lead–lithium salt process, the product being entirely free from polyethenoid fatty acids containing the penta-1 : 4-diene system.

Dorée and Pepper (*loc. cit.*) oxidised brassidic and erucic acid by using hydrogen peroxide in the presence of osmium tetroxide, also potassium permanganate in neutral and alkaline solutions; the dihydroxy- and peroxy-acids recovered corresponded to those obtained by Hilditch and other workers, from oleic and elaidic acid. By oxidising erucic acid with oxygen at 70° and 120° in the presence of a cobalt catalyst, Dorée and Pepper obtained peroxybrassidic acid (m. p. 70°), but no scission products or keto-derivatives.

In the present work brassidic acid has been oxidised at 73° and 120° with oxygen by using 0·05% uranium (as uranyl brassidate) as catalyst. At 73° the peroxide content steadily increased with time, to 0·465% of active oxygen at 36 hr., with fall in iodine and acid value. Decomposition of peroxide did not occur, and analysis confirmed the comparative stability of the hydroperoxide at this temperature.

In contrast, at 120°, a maximum peroxide content (0·29% of active oxygen, corresponding to 6·7% of brassidic hydroperoxide) was reached in 1 hr., after which the peroxide rapidly decomposed; the iodine value fell to 50% of the original value in 5 hr., and the acid value steadily decreased.

After 10 hr. at 120°, there was little evidence either of degradation of the carbon chain or of dimerisation. No monoperoxy-acids were isolated (cf. erucic acid; Dorée and Pepper, *loc. cit.*), but after saponification, dihydroxybehenic acid (8%) and a monomeric oil (72%), containing keto-hydroxy- or keto-unsaturated compounds (25%) were recovered. This oxidation of brassidic acid follows a similar course, in general, to that described for elaidic acid (Skellon and Thruston, *loc. cit.*), the initial hydroperoxide undergoing transition or decomposition mainly to a complex ketonic oil.

The formation of these ketonic complexes after decomposition of the peroxide and before polymerisation is apparently a characteristic feature in autoxidation of unsaturated fatty acids and esters.

Experimental

Preparation of Erucic Acid by Urea-complex Formation.—The mixed fatty acids (140 g.; I.V., 76; acid val., 182) from rape oil were dissolved in methanol (2500 ml.), and urea (400 g.)

added to the hot solution. On cooling, the urea complex (270 g.) separated as needles. This was warmed with dilute hydrochloric acid (1000 ml.), and the liberated fatty acids (Fraction 1; 94 g.; I.V., 76·1; acid val., 171) washed with hot water and extracted with light petroleum. Methanol (1500 ml.) was distilled from the mother-liquor; the residue, on cooling, deposited a further 110 g. of urea complexes, from which 24 g. of acids (I.V., 102; acid val., 180) were obtained. These consisted mainly of oleic and polyethenoid acids.

Lead acetate (5 g.) in boiling alcohol was added to the free acids (fraction 1; 94 g.) in ethyl alcohol and the mixture refluxed for a few moments and then set aside. The precipitated lead salts (12 g.) were converted into the fatty acids (6 g.; I.V., 30). The filtrate was again treated with lead acetate, giving insoluble lead salts, from which erucic acid (51 g., 36%) was obtained. After recrystallisation from alcohol the erucic acid had I.V., 74, acid val., 165·3.

Preparation of Erucic Acid via *the Lead Salt.*—To a boiling alcoholic solution of the mixed fatty acids (200 g.) from rape oil, lead acetate (88 g. in 100 ml. of boiling alcohol) and a few drops of acetic acid were added, and the mixture was refluxed for 2 mins. and then set aside. The lead salts were filtered off and acidified, saturated fatty acids (I.V., 21·7) separating. The filtrate was again treated with lead acetate (25 g. in 300 ml. of boiling alcohol), and the lead salts acidified, yielding erucic acid (I.V., 74), after several crystallisations of the product (40 g.) from alcohol at 0°. A further 25 g. of erucic acid were similarly obtained from the filtrate. After repeated recrystallisation from alcohol, the erucic acid had I.V., 74·5; acid val., 165·2; m. p. 33·5° (Calc. for $C_{22}H_{42}O_2$: I.V., 75·0; acid val., 165·8).

Isomerisation of Erucic Acid to Brassidic Acid.—Erucic acid was isomerised in batches to brassidic acid by use of nitrogen oxides (cf. Dorée and Pepper, *loc. cit.*). The product (yield, 65—70%) had m. p. 60° (I.V., 75°; equiv., 338).

Catalytic Autoxidation of Brassidic Acid.—The apparatus consisted of a large Pyrex tube (6 in. × 2·5 in.) fitted with an oxygen-inlet tube, thermometer, and stirrer and was fitted into a thermostatically controlled oven. Since the reaction is exothermic, the oven-temperature during oxidations was somewhat lower than that registered in the apparatus. Uranium brassidate (equivalent to 0·05% of uranium) was dissolved in the acid, and dry oxygen was bubbled through, samples of the mixture being withdrawn hourly. Carbon dioxide formation was estimated by passing the evolved gases through baryta water.

Catalytic autoxidation of brassidic acid.

At 73°.

Time, hr.	1	2	3	4	5	6	7	12	18	24	36
Active O, %	0·03	0·033	0·027	0·033	0·040	0·037	0·056	0·111	0·185	0·234	0·465
I.V.	76·5	77·4	73·0	77·8	68·1	69·2	66·7	67·4	—	68·5	58·0

At 120°.

Time, hr.	1	2	3	4	5	10
Active O, %	0·292	0·245	0·210	0·154	0·109	0·010
I.V.	64·1	59·5	51·8	47·5	41·0	36·5
Acid val.	164·8	163	163·7	162·3	158·3	—

The product of oxidation for 10 *hr. at* 120°. Only 0·02 equiv. of carbon dioxide was evolved from 1 equiv. of brassidic acid, indicating little chain-degradation. The product [Found: *M* (ebullioscopic), 335; I.V., 36·5; active oxygen, 0·010%] of 10 hr. oxidation slightly reduced Fehling's solution. A portion (13 g.) was warmed with alcoholic potassium hydroxide (10 g. in 50 ml. of alcohol), and the alcohol then distilled off. After acidification and cooling, the brown product was repeatedly extracted with cold light petroleum (b. p. 40—60°). Removal of solvent and recrystallisation of the residue (2·6 g.) from alcohol gave unchanged brassidic acid (0·8 g.), m. p. 60°, acid val., 167·3. On removal of alcohol from the filtrate, a light brown oil (acid val., 155; I.V., 42·3) remained, which did not reduce Fehling's solution. The fraction, insoluble in cold light petroleum, was extracted with ether giving, on removal of solvent, a dark-brown, waxy solid (4·1 g.) from which unchanged brassidic acid and a residual oil (acid val., 174·4; I.V., 34·4) were recovered. Recrystallisation of the residue from the ether extraction gave dihydroxybehenic acid, m. p. and mixed m. p. 132° (Found: acid val., 148. Calc. for $C_{22}H_{44}O_4$: acid val., 150).

The product from a similar oxidation was examined portionwise for hydroxyketo-derivatives and peroxybrassidic acid. As a modification of King's method (*J.*, 1936, 1788) for the isolation of hydroxyketostearic acids, a solution of the product (5 g.) in chloroform (50 ml.) was kept below 0° for 24 hr.; no solid separated. The chloroform was therefore removed, the residue taken up in light petroleum (b. p. 40—60°; 200 ml.), and, after 24 hr. at −10°, the residue was separated

and again treated with chloroform and light petroleum. The product (I.V., 19; acid val., 126) readily reduced Fehling's solution, indicating a hydroxy-ketone (acyloin) or an unsaturated ketonic derivative. The remainder of the oxidation product (10 g.) was examined for peroxybrassidic acid, by dissolution in alcohol and cooling at 0° for 48 hr. The product (1·9 g.), m. p. 60° (I.V., 66·1; acid val., 148·6; mean equiv., 376), was not identifiable with peroxybrassidic acid (Calc. for $C_{22}H_{44}O_3$: equiv., 356) and probably consisted of unchanged brassidic acid, mixed with the ketol derivative (Calc. $C_{22}H_{42}O_4$: equiv., 370).

The oil obtained on evaporation of the alcoholic filtrate had I.V., 37, acid val., 140, and reduced Fehling's solution (Found: CO, 1·9%). Extraction with cold light petroleum (b. p. 40—60°) gave a pale oil [I.V., 39·4; acid val., 99; *M* (ebullioscopic), 232] whilst the insoluble residue (I.V., 23·1; acid val., 125) also strongly reduced Fehling's solution.

The oily oxidation complexes of brassidic acid (and similar products of other oxidised monoethenoid fatty acids), unlike pure ketols formed by oxidation with neutral permanganate, do not form crystalline dinitrophenylhydrazones or semicarbazones.

Modified special methods of determining CO in oxidised fatty acids, esters, and parent fats are under investigation.

ACTON TECHNICAL COLLEGE, ACTON, W.3. [*Received, October 30th*, 1952.]

295. *A Spectrophotometric Study of the Iron(III) Chloro-complexes.*

By G. A. GAMLEN and D. O. JORDAN.

The nature of the chloro-complexes of iron(III) in concentrated hydrochloric acid solution is discussed, and from a consideration of previous data and some new results it is concluded that the highest chloro-complex formed has the formula $FeCl_4^-$.

Values of the third and fourth association constants are obtained together with values of $\varepsilon_{FeCl_4^-}$, ε_{FeCl_3}, and $\varepsilon_{FeCl_2^+}$ at wave-lengths in the range 220—440 mμ. The values of the extinction coefficient in the range 400—440 mμ are in agreement with values given previously even though the calculations are based on different assumptions.

THE association of the Fe^{3+} ion with chloride ions in solutions of hydrochloric acid may be represented, according to Bjerrum's theory of complex formation (Thesis, Copenhagen, 1941) and with neglect of the hydration of the metal and complex ions, as follows:

$$Fe^{3+} + Cl^- \rightleftharpoons FeCl^{2+} \quad K_1 = a_{FeCl^{2+}}/a_{Fe^{3+}} \cdot a_{Cl^-} \quad (1)$$

$$FeCl^{2+} + Cl^- \rightleftharpoons FeCl_2^+ \quad K_2 = a_{FeCl_2^+}/a_{FeCl^{2+}} \cdot a_{Cl^-} \quad (2)$$

$$FeCl_2^+ + Cl^- \rightleftharpoons FeCl_3 \quad K_3 = a_{FeCl_3}/a_{FeCl_2^+} \cdot a_{Cl^-} \quad (3)$$

$$FeCl_3 + Cl^- \rightleftharpoons FeCl_4^- \quad K_4 = a_{FeCl_4^-}/a_{FeCl_3} \cdot a_{Cl^-} \quad (4)$$

These complexes have already been investigated both electrometrically and spectrophotometrically, but although considerable evidence has been accumulated concerning the nature of the highest complex and the values of K_1 and K_2, neither are there accurate data for K_3 and K_4 nor has the spectrum for each complex in the ultra-violet, which are of greater significance than the visible spectra, been recorded. Bent and French (*J. Amer. Chem. Soc.*, 1941, **63**, 568), using the $FeCNS^{2+}$ ion as a coloured indicator for the concentration of free Fe^{3+} ions, obtained a value for K_1, but owing to their neglect of the higher complexes and to the possible formation of mixed chloro- and thiocyanato-complexes, their result must be regarded as approximate. Rabinowitch and Stockmayer (*ibid.*, 1942, **64**, 335), from an extensive spectrophotometric study of the spectra of ferric perchlorate solutions containing hydrochloric acid, obtained values for K_1 and K_2 and gave an estimate of the value of K_3. They also obtained the spectra for the hydrated ferric ion, Fe^{3+} (aq.), and of the three species $FeCl^{2+}$, $FeCl_2^+$, and $FeCl_3$ over the range 400—460 mμ. A similar study, but in the ultra-violet region of the spectrum, was made by Olerup (Thesis, Lund, 1944; *Svensk Kem. Tidskr.*, 1943, **55**, 324), who also obtained values for K_1 and K_2 and an estimate of the value of K_3 for the complexes in 2*M*-perchloric

acid solution, which were in reasonable agreement with Rabinowitch and Stockmayer's results (*loc. cit.*).

The spectra of ferric chloride or perchlorate in solutions of various concentrations of hydrochloric acid have also been recorded by Ábrahám (*Acta Univ. Szeged*, 1938, *b*, **6**, 272), Kiss, Ábrahám, and Hegedüs (*Z. anorg. Chem.*, 1940, **244**, 98), and Metzler and Myers (*J. Amer. Chem. Soc.*, 1950, **72**, 3776), but no attempt was made by these authors to obtain either the association constants or the spectra of the individual ionic species existing in solution.

In this communication we describe the determination of the association constants K_3 and K_4 and of the spectra of $FeCl_2^+$, $FeCl_3$, and $FeCl_4^-$. These results, taken with those of Rabinowitch and Stockmayer (*loc. cit.*) and of Olerup (*loc. cit.*), thus completely describe the nature of the chloro-complexes of the ferric ion in solution.

Theoretical Discussion.—Solutions of ferric chloride in water contain, in addition to the chloro-complexes, the hydroxy-complexes $Fe(OH)^{2+}$, $Fe(OH)_2^+$, and $Fe(OH)_3$ which have already been extensively investigated (Lamb and Jacques, *J. Amer. Chem. Soc.*, 1938, **60**, 967, 1215; Rabinowitch and Stockmayer, *loc. cit.*; Bray and Hershey, *J. Amer. Chem. Soc.*, 1934, **56**, 1889; Brosset, *Svensk Kem. Tidskr.*, 1941, **53**, 434; Olson and Simonson *J. Chem. Phys.*, 1949, **17**, 1322; Siddall and Vosburgh, *J. Amer. Chem. Soc.*, 1951, **73**, 4270). According to Rabinowitch and Stockmayer (*loc. cit.*) the absorption by the hydroxy-complexes is sufficiently large to interfere with the spectra of the chloro-complexes even when the former are present in very small quantities. It is therefore necessary to employ a strong non-complexing acid medium when the lower chloro-complexes are studied in order to prevent the formation of the hydroxy-complexes, and perchloric acid is generally used for this purpose (see Rabinowitch and Stockmayer, *loc. cit.*). Recently, Sutton (*Nature*, 1952, **169**, 71) has shown that a ferric ion–perchlorate ion pair is formed in solutions of 10^{-4}M-ferric perchlorate in perchloric acid of concentration between 1 and 7M. The value of the constant (K_p) for the association

$$Fe^{3+} + ClO_4^- \rightleftharpoons FeClO_4^{2+}$$

is, however, so small compared with the values of K_1 that have been recorded that the latter values are unlikely to be in serious error owing to the ion-pair formation [$K_1 = 30$ (Rabinowitch and Stockmayer, *loc. cit.*), $K_p = 0{\cdot}47$ (Sutton, *loc. cit.*)].

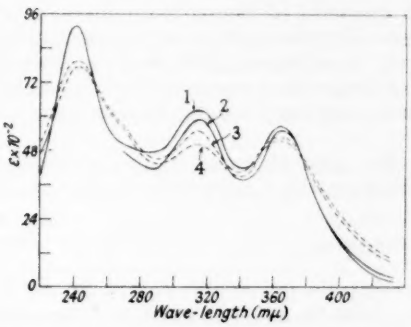
Formula of the highest chloro-complex. Direct evidence for the nature of the highest complex formed is not easy to obtain, but information can be obtained from experiments in which the aqueous solution is extracted with a suitable organic solvent, and the nature of the extracted species determined by direct analysis. Comparison can also be made between the absorption spectra of the extract and of the original aqueous solution. Using these methods, Nachtrieb and Conway (*J. Amer. Chem. Soc.*, 1948, **70**, 3547) showed that the chloro-complex extracted from solutions containing 2—8M-hydrochloric acid has the formula $HFeCl_4$, and that at concentrations above 8M, the molar ratio of HCl to $FeCl_3$ rises to 4. Nachtrieb and Conway were unable to decide whether this observation should be interpreted as evidence for the formation of higher complexes of formula H_2FeCl_5, H_3FeCl_6, etc., or as a salting-in effect caused by the $FeCl_3$. However, they point out that the ethereal extract of the solution of the complex in 7·5M-hydrochloric acid obeys Beer's law over the concentration range 0·01—0·4 mole/l. of iron at various wave-lengths in the visible region of the spectrum, which suggests the existence of only a single species in this solution. Furthermore, the spectrum of this extract is identical with that of extracts from solutions containing hydrochloric acid of concentration greater than 8M, in which up to 3 molecules of hydrochloric acid are associated with one molecule of ferric chloride. This evidence would appear to indicate that $HFeCl_4$ is the highest complex formed. This result has been confirmed by Myers, Metzler, and Swift (*J. Amer. Chem. Soc.*, 1950, **72**, 3767), who also showed that there is a great similarity between the spectra of the chloro-complexes present in aqueous solutions of concentrated hydrochloric acid (*ca.* 11·5M) and that of the complex extracted therefrom by *iso*propyl ether (see also Metzler and Myers, *loc. cit.*) and which was shown to have the formula $HFeCl_4$.

A spectrophotometric study of solutions of ferric perchlorate in ethyl alcohol containing

lithium chloride (10^{-2} to 1M), taken in conjunction with the results of conductometric titration, led Brealey, Evans, and Uri (*Nature*, 1950 **166**, 959) to conclude that the ion $FeCl_4^-$ is formed quantitatively under these conditions and that no higher complex occurs. The spectrum of the chloro-complex under these conditions in ethyl alcohol is very similar to that obtained in aqueous solutions of hydrochloric acid at a concentration of 11·5M, as shown in Fig. 1, and it would therefore appear that the same complex predominates in both solvents. Brealey and Uri (*J. Chem. Phys.*, 1952, **20**, 257) have attempted to verify the formula $FeCl_4^-$ for the highest complex by plotting $\log\{[FeCl_4^-]/[FeCl_3]\}$, evaluated from their absorption spectra data on alcoholic solutions, against $\log [LiCl]$. A straight line of slope approximately 1·4 was obtained, and Brealey and Uri attribute the deviation from the theoretical slope of unity to partial solvolysis of $FeCl_3$, an explanation which is equivalent to suggesting a difference in the co-ordination number of $FeCl_4^-$ and $FeCl_3$ (see below).

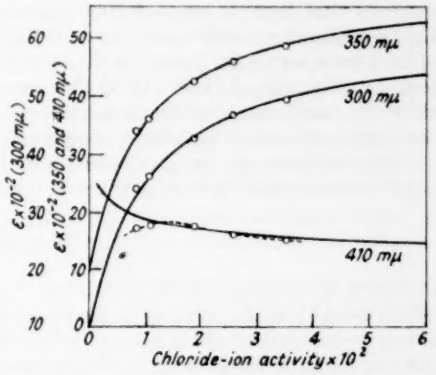
More positive evidence concerning the nature of the highest complex has been obtained by Friedman (*J. Amer. Chem. Soc.*, 1952, **74**, 5) who prepared salts of the type $M'M'''Cl_4$, where M′ is K^+, Cs^+, or NH_4^+ and M‴ is Fe^{3+} or Al^{3+}. The absorption spectra of the iron

FIG. 1. *Absorption spectra of ferric chloride in solutions of high chloride-ion concentration.*



Full line: dry ethyl alcohol as solvent. Broken line: water as solvent. 1, 3·62M-LiCl; 2, 0·31M-LiCl; 3, LiCl–HCl *mixture, chloride-ion concentration* 12·5M; 4, 11·5M-HCl.

FIG. 2. *Variation of extinction coefficient with chloride-ion activity at various wave-lengths.*



Open circles represent experimental points. Full curves are calculated from equation (13).

salts in the solid state and in solution in ethylene bromide and ethyl ether are very similar and closely resemble the spectra of ferric chloride in 11·5M-hydrochloric acid and of the ether extracts therefrom.

We have attempted the preparation of higher chloro-complexes than $FeCl_4^-$ in both alcoholic and aqueous solution. In view of the ease with which the $FeCl_4^-$ ion is formed in ethyl alcohol (Brealey, Evans, and Uri, *loc. cit.*), we studied the spectrum of ferric chloride solutions in ethyl alcohol saturated with lithium chloride (*ca.* 3M). At this concentration of chloride, which is 300 times that required for the almost quantitative formation of $FeCl_4^-$, the spectrum is identical in form with that at 0·1M-lithium chloride, which would appear strong evidence for the non-formation of a higher complex (Fig. 1). That the values of the extinction coefficient are slightly greater for the higher chloride concentrations is best explained on the basis of a shift in the equilibrium represented by equation (4) to favour the formation of $FeCl_4^-$.

The behaviour of aqueous solutions of ferric chloride is very similar. In very concentrated chloride solutions, obtained by saturating concentrated hydrochloric acid with lithium chloride, the spectrum of the chloro-complex remained almost identical with that obtained in the solution of concentrated hydrochloric acid alone (Fig. 1), there being a slight intensification of the characteristics of the $FeCl_4^-$ spectrum but a non-appearance of any new features. This result is a confirmation of the work of Friedman (*loc. cit.*), who obtained

the spectrum of the chloro-complex existing in 16M-hydrochloric acid prepared by saturating the concentrated acid with hydrogen chloride under pressure. These results are again best explained by a small shift in the equilibrium favouring an increase in the concentration of $FeCl_4^-$ rather than by the formation of any new species.

Further support for the conclusion that the $FeCl_4^-$ ion is the limiting complex is given by the variation of the extinction coefficients with chloride activity. At all wave-lengths ε tends to a limiting value at the highest chloride-ion activity used (Fig. 2). It is unlikely that this would be so if a fifth complex were formed unless this complex had ε values close to those for $FeCl_4^-$, but in view of the relatively high ε values of $FeCl_4^-$ over the range 220—380 mμ it is probable that there would be at least one region of the spectrum in which the value of ε for the fifth complex was lower than for $FeCl_4^-$. At wave-lengths greater than 400 mμ there is a small maximum (see broken line in Fig. 2) in the value of ε at relatively low chloride-ion activities (*ca.* $1{\cdot}3 \times 10^2$) due to ε_{FeCl_3} being greater than $\varepsilon_{FeCl_4^-}$ at these wave-lengths. At high values of the chloride-ion activity, however, ε still tends to a limiting value.

There thus appears to be strong presumptive evidence that the $FeCl_4^-$ ion is the limiting chloro-complex of the ferric ion. This conclusion does not in itself indicate that the co-ordination number of iron in this complex is four and not six, but Friedman (*loc. cit.*) has shown that a change of solvent has very little effect on the spectrum of $KFeCl_4$, which suggests that there is no co-ordination of solvent molecules to the central atom and that the co-ordination number of iron in $FeCl_4^-$ is four. The change in co-ordination number of iron from six in Fe^{3+} and $FeCl^{2+}$ to four in $FeCl_4^-$ is in keeping with the generalisation (see, *e.g.*, Nyholm, *J.*, 1952, 1257) that metals having more than one co-ordination number show the maximum co-ordination number in cationic complexes and this decreases through non-ionic compounds to anionic complexes.

Determination of the association constants. The general form of the association equilibrium, activities being written in terms of concentrations and activity coefficients, is

$$K_n = \frac{[FeCl_n^{3-n}]}{[FeCl_{n-1}^{4-n}][Cl^-]} \cdot \frac{f_{FeCl_n^{3-n}}}{f_{FeCl_{n-1}^{4-n}} f_{Cl^-}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

in which the activity coefficients $f_{FeCl_n^{3-n}}$ and $f_{FeCl_{n-1}^{4-n}}$ are not known except for $FeCl_3$, which Nachtrieb and Fryxell (*J. Amer. Chem. Soc.*, 1952, **74**, 897) find to be approximately 1·0 at concentrations of $FeCl_3$ up to 0·1M in 5M-hydrochloric acid saturated with $FeCl_2,4H_2O$. An exact treatment without the introduction of non-thermodynamic assumptions is therefore not possible. The approximation generally made (see Bjerrum, *Kgl. Danske Videnskab. Selskab., Mat.-fys. Medd.*, 1946, **22**, No. 18; Näsänen, *Acta Chem. Scand.*, 1950, **4**, 140, 816) is to assume that a single mean activity coefficient, F, may be used to replace the activity coefficient term in equation (5), *i.e.*,

$$\frac{1}{F} = \frac{f_{FeCl^{2+}}}{f_{Fe^{3+}} f_{Cl^-}} = \frac{f_{FeCl_2^+}}{f_{FeCl^{2+}} f_{Cl^-}} = \frac{f_{FeCl_3}}{f_{FeCl_2^+} f_{Cl^-}} = \frac{f_{FeCl_4^-}}{f_{FeCl_3} f_{Cl^-}} \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

This approximation is equivalent to assuming that

$$f_{FeCl_n^{3-n}}/f_{FeCl_{n-1}^{4-n}} = C \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where C is a constant, *i.e.*, that the activity coefficients of the complexes change uniformly throughout the series. As Bjerrum (*loc. cit.*) points out, this is not an unreasonable assumption for solutions of high ionic strength for which chemical structure rather than charge determines the value of the activity coefficients.

Bjerrum (*loc. cit.*) then expresses F by the equation

$$\log F = A + B[Cl^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

in which A and B are constants for a particular system. This equation is of the form required by the extensions of the Debye–Hückel theory for concentrated solutions, and corresponds to the approximate empirical equations which hold for the activity coefficients of hydrochloric acid and calcium chloride at concentrations greater than 3N, *viz.*,

$$\left.\begin{aligned} \log f_{HCl} &= -0{\cdot}42 + 0{\cdot}18[Cl^-] \\ \log f_{CaCl_2} &= -0{\cdot}55 + 0{\cdot}20[Cl^-] \end{aligned}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

For the chloro-complexes of the cupric ion, Bjerrum (*loc. cit.*) was able to determine the constant B in equatio (8) since at a wave-length of 436 mμ, only the tetrachloro-complex absorbs; hence the concentration of this complex could be determined from Beer's law and B could then be calculated by using an extension of Bodländer's equation. The values of the association constants could, however, still not be calculated with certainty since only an approximate estimate of the value of the constant A could be made. With the ferric chloride system, this procedure cannot be followed since there is no wave-length at which only one of the ionic species absorbs. We shall therefore make our calculations of the association complexes and of the extinction coefficients of the individual ions on the basis that in equation (7), $C = 1$, a procedure which involves no new assumptions other than those already made by Bjerrum (*loc. cit.*). Then by introducing the "Guggenheim assumption" that $f_{Cl^-} = f_{HCl}$ we can rewrite equation (5) in the form

$$K_n' = \frac{[FeCl_n^{3-n}]}{[FeCl_{n-1}^{4-n}][Cl^-]} \cdot \frac{1}{f_{HCl}} \quad \ldots\ldots\ldots \quad (10)$$

in which we replace K_n by K_n' for the association constant, since non-thermodynamic assumptions have been introduced.

That this procedure may give values of the association constant (K_n') not significantly different from that of the true constant (K_n) is shown by the results of Bjerrum (*loc. cit.*) and of Näsänen (*loc. cit.*) for the chloro-complexes of the cupric ion. For this system it was found that for solutions containing hydrochloric acid $B = 0{\cdot}20$ (Bjerrum) and $0{\cdot}21$ (Näsänen), and for solutions containing calcium chloride $B = 0{\cdot}21$ (Bjerrum). The close agreement between these values and the values of B in equation (9), taken with the fact that Bjerrum concludes that the value of A in concentrated solutions of various chlorides must be between 0 and $-0{\cdot}5$, shows that the use of the equation corresponding to (10) for the chloro-complexes of the cupric ion would be justifiable for that system. The similarity between the cupric chloride and the ferric chloride systems suggests that a similar procedure may lead to values close to the true values of the association constants for the chloro-complexes of the ferric ion.

The experimental difficulties attendant on the determination of the association constants increase considerably as the number of complexes increases. This is particularly true if the formation constants of the higher complexes are small, as it is then necessary to make measurements in high and varying concentrations of the co-ordinating ion. The method of corresponding solutions has frequently been used for obtaining association constants from spectral data (Bjerrum, *Kgl. Danske Videnskab. Selskab., Mat.-fys. Medd.*, 1944, **21**, No. 4), and a modification of this method was used by Olerup (Thesis, Lund, 1944; *Svensk Kem. Tidskr.*, 1943, **55**, 324) for the determination of K_1 and K_2 for the chloro-complexes of iron. The method is limited in its application, however, to relatively dilute solutions of the co-ordinating ion, since it is dependent on the accurate determination of the difference between the total ligand concentration ([A]) and the concentration bound to the central ion (C_A). In concentrated solutions of ligand (greater than 3N) and very dilute solutions of the central ion (*ca.* 0·001N) such as must be employed for the formation of the higher chloro-complexes of iron, C_A is negligibly small compared with [A] and the method cannot be used.

An alternative method, which has been used in the present work, is to study the variation of the extinction coefficient with ligand concentration. This method has frequently been used for the determination of the first association constants, but the analysis of the data becomes difficult when several complexes are present. However, by introducing certain simplifying assumptions which appear to be justified in the present case, the constants can be evaluated.

Since we have shown that $FeCl_4^-$ is the highest complex formed, and as there is little variation of the extinction coefficient (ε_{Fe}) with chloride concentration in the concentration range 8—11·35M (Fig. 2), it appears probable that only the species $FeCl_3$ and $FeCl_4^-$ are present in these solutions. On the basis of this assumption, equations similar to those derived by Olson and Simonson (*J. Chem. Phys.*, 1949, **17**, 1322) can now be obtained.

We have assumed that $\Sigma Fe = [FeCl_4^-] + [FeCl_3]$, and it follows that for 1-cm. cells the optical density is given by

$$D = [FeCl_4^-]\varepsilon_{FeCl_4^-} + [FeCl_3]\varepsilon_{FeCl_3} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

and putting (4), in view of (10), in the form

$$k_4' = 1/K_4' = [FeCl_3][Cl^-]f_{HCl}/[FeCl_4^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

we obtain

$$\varepsilon_M(k_4' + [Cl^-]f_{HCl}) = [Cl^-]f_{HCl}\varepsilon_{FeCl_4^-} + k_4'\varepsilon_{FeCl_3} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

in which $\varepsilon_M = D/\Sigma Fe$.

Equation (13) contains three unknowns k_4', $\varepsilon_{FeCl_4^-}$, and ε_{FeCl_3}. From measurements at three different chloride concentrations in the range 8—11·35N, and solving the three simultaneous equations, we obtain.

$$k_4' = \frac{\varepsilon'_M A_1(A_2 - A_3) + \varepsilon_M'' A_2(A_3 - A_1) + \varepsilon_M''' A_3(A_1 - A_2)}{\varepsilon_M'(A_2 - A_3) + \varepsilon_M''(A_3 - A_1) + \varepsilon_M'''(A_1 - A_2)} \quad . \quad . \quad . \quad (14)$$

where ε_M', ε_M'', ε_M''' and A_1, A_2, A_3 are the observed average extinction coefficients and chloride activities, respectively, for the three solutions.

From the value of k_4' thus determined, $\varepsilon_{FeCl_4^-}$ and ε_{FeCl_3} could be found in a similar way from measurements on two solutions of different chloride-ion activity. We have, however, preferred an alternative method. The plot of ε_M against $[Cl^-]f_{HCl}$ will give, as is evident from equation (13), a rectangular hyperbola (see Fig. 2) with asymptotes $x = -k_4'$ and $y = \varepsilon_{FeCl_4^-}$, the intercept on the ordinate being ε_{FeCl_3}. Knowing k_4', however, we may plot the function $\varepsilon_M(k_4' + [Cl^-]f_{HCl})$ against $[Cl^-]f_{HCl}$, which should give a straight line of slope $\varepsilon_{FeCl_4^-}$ and an intercept of $k_4'\varepsilon_{FeCl_3}$. The value of $\varepsilon_{FeCl_4^-}$ may be obtained from the slopes of the lines with good accuracy, but the value of the intercept, which gives ε_{FeCl_3}, is very dependent on the " best " straight line chosen. The value of the intercept was therefore calculated by the method of least squares. This method may be extended to less concentrated solutions of hydrochloric acid where a third complex $FeCl_2^+$ will also be present. We then have, ultimately,

$$\varepsilon_M\{k_3'k_4' + k_4'[Cl^-]f_{HCl} + ([Cl^-]f_{HCl})^2\} = ([Cl^-]f_{HCl})^2\varepsilon_{FeCl_4^-} + k_4'[Cl^-]f_{HCl}\varepsilon_{FeCl_3} + \varepsilon_{FeCl_2^+} \quad . \quad (15)$$

in which k_3' is defined in a similar manner to k_4', *viz.*,

$$k_3' = [FeCl_2^+][Cl^-]f_{HCl}/[FeCl_3] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

and in which k_3' and $\varepsilon_{FeCl_2^+}$ are the only unknowns. Values of these may therefore be obtained from measurements at two different chloride activities.

Results and Discussion.—The spectra of solutions of ferric chloride at various concentrations of hydrochloric acid and at a concentration of ferric chloride of approximately 0·002M are shown in Fig. 3. The spectra resemble those published by Metzler and Myers (*loc. cit.*). The plot of the function $\varepsilon_M(k_4' + [Cl^-]f_{HCl})$ against $[Cl^-]f_{HCl}$ [equation (13)] is given in Fig. 4 for four typical wave-lengths, and the very good straight lines obtained show that the assumption that only two complexes are present in solutions of hydrochloric acid of concentration greater than 8·0M is justified. The five points on each straight line refer to measurements on solutions of concentration 8·20, 8·65, 9·86, 10·60, and 11·35M in hydrochloric acid, and values of K_4' have been calculated from results obtained at 10 mμ intervals between 260 and 400 mμ. Values of K_3' were similarly calculated at different wave-lengths from measurements on solutions containing hydrochloric acid of concentration 5·08 and 3·33M by means of equation (15). The mean values of K_3' and K_4' are given in the Table along with the values of K_1, K_2, and K_3 given by Rabinowitch and Stockmayer (*loc. cit.*), and by Olerup *locc. cit.*).

Formation constants of the iron(III) *chloro-complexes.*

K_1	K_2	K_3	K_4'	Conditions *	Author
4·2	1·3	0·04	—	$I = 1$, $T = 26·7°$	Rabinowitch and Stockmayer
30	4·5	0·1	—	$I = 0$, $T = 25°$	
5·7	2·0	0·87	—	2M-$HClO_4$, $I = 2$, $T = 20°$	Olerup
		K_3'			
—	—	0·73	0·0105	$I = 0$, $T = 20°$	This paper

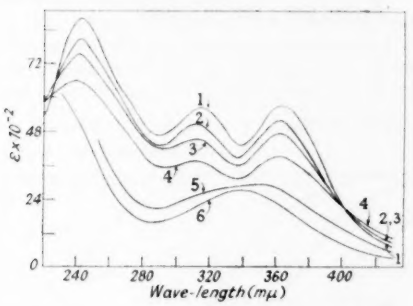
* I = Ionic strength.

A feature of these results is the apparently low value of K_4', and the reason for this result may be sought by calculating the values of the " ligand effect " by Bjerrum's method (Thesis, Copenhagen, 1941). In this treatment, the ratio of the consecutive formation constants is regarded as the product of the statistical (S) and ligand (L) effects, *viz.*,

$$\log (K_n/K_{n+1}) = S_{n,n+1} + L_{n,n+1} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

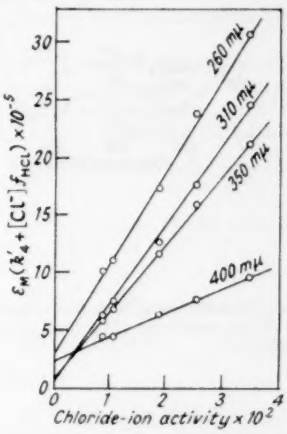
where $S = \log [(N - n + 1)(n + 1)/(N - n)n]$. Calculation of L for a co-ordination number (N) of 6, the values 30, 4·5, 0·73, and 0·0105 being used for K_1, K_2, K_3, and K_4, respectively, gives $L_{1,2} = 0{\cdot}44$, $L_{2,3} = 0{\cdot}52$, and $L_{3,4} = 1{\cdot}59$, or for a co-ordination number of four $L_{3,4} = 1{\cdot}41$. For a given series of complexes the ligand effect should be a constant, and Bjerrum (Thesis, Copenhagen, 1941; *Kgl. Danske Videnskab. Selskab., Mat.-fys. Medd.*, 1946, **22**, No. 18) has shown this to be so for several systems. Furthermore, when the co-ordinating group is an ion, the ligand effect should be a function of the electrostatic work done in changing the complex from, for example, $FeCl_n^{3-n}$ to $FeCl_{n+1}^{2-n}$, and from the theory of the electrostatic field effect (see N. Bjerrum, *Z. physikal. Chem.*, 1923, **106**, 219;

FIG. 3. *Variation of extinction coefficient with wave-length for various concentrations of hydrochloric acid at constant concentration of ferric chloride* (0·002M).



1, 11·35M; 2, 10·60M; 3, 9·86M; 4, 8·65M; 5, 5·08M; 6, 3·33M.

FIG. 4. *Variation of the function* $\varepsilon_M(k'_4 + [Cl^-]f_{HCl})$ *with chloride-ion activity for four typical wave-lengths.*



Kirkwood and Westheimer, *J. Chem. Phys.*, 1938, **6**, 506, 513), we may write for a singly charged co-ordinating ion

$$L_{n,n+1} = e^2/DakT \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

where e is the electronic charge, k the Boltzmann constant, T the temperature, D the effective dielectric constant, and a the distance between the charged groups. In arriving at equation (18) we have assumed that the " Rest effect " (Bjerrum, Thesis, Copenhagen, 1941) is negligibly small and that the iron(III) chloro-complexes are ionic, as suggested by the magnetic moment of $FeCl_4^-$ determined by Nyholm (*J.*, 1950, 851) and by Metzler and Myers (*loc. cit.*). Calculation of a from $L_{1,2}$ and $L_{2,3}$, D for water being taken as 78, gives the values 7 and 6 Å. The good agreement between these values reflects the agreement between $L_{1,2}$ and $L_{2,3}$ and the values, although somewhat high, are of the order of magnitude to be expected for the distance between the chloride ions in $FeCl_3$. A similar calculation for $L_{3,4}$ leads to a very low and improbable value for a (2 Å). It would therefore appear that the values of $L_{1,2}$ and $L_{2,3}$, and hence of K_1, K_2, and K_3, may be regarded as normal values, the variation of the association constants being of the order expected. On the other hand, $L_{3,4}$ is higher and K_4 lower (relative to K_3) than would be predicted. Such behaviour may be attributed to a change in the co-ordination number of the central ion from six to four at $FeCl_3$, *i.e.*, a change on the addition of Cl^- from $FeCl_3(H_2O)_3$ to

$FeCl_4^-$ as is suggested by Friedman's results (*loc. cit.*) discussed above. If this conclusion is correct, the values of $L_{3,4}$, obtained above, can have no theoretical significance, since in the ratio K_3/K_4 the two association constants refer to different structures.

The values of $\varepsilon_{FeCl_4^-}$, ε_{FeCl_3}, and $\varepsilon_{FeCl_2^+}$ obtained by equations (13) and (15), together with the values of $\varepsilon_{FeCl^{2+}}$ and $\varepsilon_{Fe^{3+}}$ taken from Olerup's results (Thesis, Lund, 1944) are given in Fig. 5. In the range 400—440 mμ Rabinowitch and Stockmayer's values (*loc. cit.*) for ε_{FeCl_3} and $\varepsilon_{FeCl_2^+}$ are also shown, and the agreement of the two sets of results over this range is very satisfactory, particularly in view of the different assumptions made in the two methods of calculation. This confirmation of Rabinowitch and Stockmayer's value of ε_{FeCl_3} at 400 mμ invalidates Olerup's criticism (*loc. cit.*, p. 76) that this value was too high. The similarity of the spectra of $FeCl^{2+}$ and $FeCl_2^+$, which both have a maximum

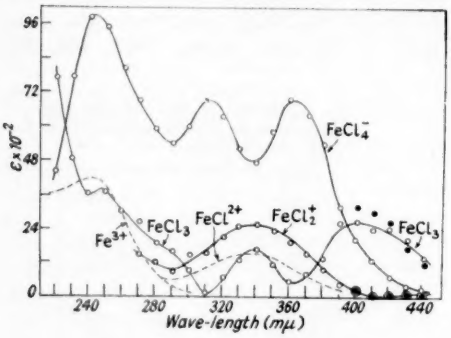


FIG. 5. *Molecular extinction coefficients at various wave-lengths for the species* $FeCl_4^-$, $FeCl_3$, $FeCl_2^+$, $FeCl^{2+}$, *and* Fe^{3+}. ○ *Values calculated from results in Fig.* **3** *by authors.* ● *Rabinowitch and Stockmayer's results. Broken line: Olerup's data.*

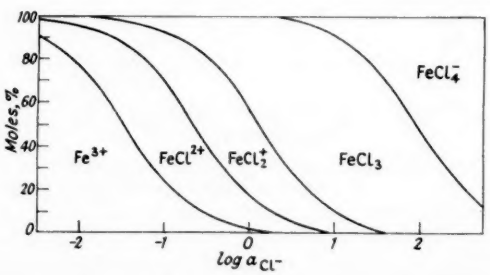


FIG. 6. *Distribution of the ferric ion among the chloro-complexes at various chloride-ion activities.*

absorption at 340 mμ, although $\varepsilon_{FeCl_2^+} > \varepsilon_{FeCl^{2+}}$, and the broad absorption band of $FeCl_3$ in the range 380—440 mμ, confirms Metzler and Myers's qualitative predictions (*loc. cit.*). The calculated spectra of $FeCl_4^-$ and $FeCl_3$ given in Fig. 4 are in general agreement with those of Brealey and Uri (*loc. cit.*) for alcoholic solutions containing perchloric acid apart from the small maximum in ε_{FeCl_3} which we obtain at 340 mμ. The values of the extinction coefficients given by Brealey and Uri are, however, somewhat higher than those obtained for aqueous solutions.

From the values of the four constants, the distribution of the ferric ion among the four complexes may be calculated, and this is shown diagrammatically in Fig. 6.

The extension of this method to more dilute solutions of hydrochloric acid in order to obtain values of K_1', K_2', and $\varepsilon_{FeCl^{2+}}$ is rendered difficult by the formation of the hydroxy-complexes. If these are eliminated by the addition of perchloric acid to give a concentration of 3M, the dissociation constants at $I = 0$ cannot be determined since the activities of hydrochloric acid in perchloric acid solutions are not known. We have attempted to obtain values at constant ionic strength by the addition of sodium perchlorate, but this produces a marked shift in the absorption curve to higher ε values, an effect which has also been observed by Olson and Simonson (*loc. cit.*).

Experimental

Spectroscopic Measurements.—Spectra were measured at 20° ± 1° by means of a Unicam S.P. 500 spectrophotometer and matched 2, 10, 20, and 40 mm. cells.

Preparation of Materials.—Aqueous solutions of ferric perchlorate were prepared by Lindstrand's method (*Z. anorg. Chem.*, 1936, **230**, 187). Crystals of hydrated ferric perchlorate were prepared by adding 5 g. of reduced iron to 45 ml. of 60% perchloric acid (3 ml. excess) in an evaporating basin (addition of acid to iron gives a brown sludge which is difficult to dissolve). To ensure that the iron was fully oxidised, 2 ml. of hydrogen peroxide (20-vol.) were added, and the solution heated to 70°. The solution was filtered (No. 3 sintered-glass filter), evaporated until crystallization occurred and fumes of perchloric acid were evolved, and placed in a vacuum-desiccator (P_2O_5; NaOH). The crystals as first prepared were light brown, but on standing *in vacuo* over P_2O_5 for four weeks they changed through yellow to white with a mauvish tinge. The yellow crystals had the composition $Fe(ClO_4)_3,10H_2O$.

Solutions of anhydrous ferric perchlorate in dry ethyl alcohol were prepared by reaction of a solution of anhydrous silver perchlorate (Hill, *J. Amer. Chem. Soc.*, 1921, **43**, 254) in a closed system with the stoicheiometric quantity of a solution of anhydrous ferric chloride in dry alcohol. They were deep red and all attempts to promote crystallisation failed.

The ferric chloride was of A. R. quality and was generally purified by sublimation although this did not appear to be essential. The perchloric acid and hydrochloric acid were of A.R. quality and the lithium chloride of reagent quality. Absolute ethyl alcohol suitable for spectroscopic measurements was prepared either by the calcium method or by the aluminium amalgam method.

The concentration of the solutions containing ferric chloride and hydrochloric acid was determined by gravimetric estimation of the iron and chloride. The values of the activity coefficients for hydrochloric acid in concentrated aqueous solutions were taken from Akerlöf and Teare's data (*J. Amer. Chem. Soc.*, 1937, **59**, 1855).

We wish to thank Dr. J. Chatt for helpful criticism and Mrs. J. Lewis for assistance with the numerical computation.

The University, Nottingham. [*Received, October 31st*, 1952.]

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296. *The Effect of Solvents on the Tautomeric Equilibria of 4-Arylazo-1-Naphthols and the* ortho-*Effect.*

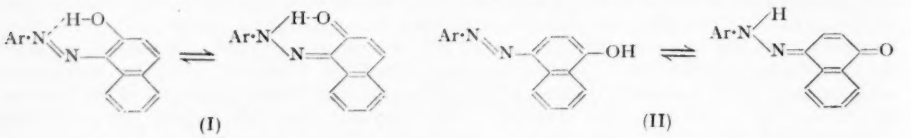
By A. Burawoy and A. R. Thompson.

The electronic spectra of 4-arylazo-1- and 1-arylazo-2-naphthols in various solvents have been determined. The differences in the effects of solvents and of *ortho*-substituents on the tautomeric equilibria observed in these two series are discussed. They originate mainly in the ability of both tautomers of the 4-arylazo-1-naphthols (in contrast to those of the 1-arylazo-2-naphthols) to form external hydrogen bonds with suitable solvents. The different strength of these bonds in the azo- and phenylhydrazone tautomers is shown to influence considerably the equilibrium constants. The inhibition of external hydrogen-bond formation by *ortho*-substituents in the phenylhydrazone tautomers is mainly responsible for their surprisingly small concentrations in solvents such as water, ethyl alcohol and acetic acid.

Investigation of the electronic spectra of 1-arylazo-2-naphthols has shown that they exist in solution as tautomeric equilibria (I) (Burawoy, Salem, and Thompson, *J.*, 1952, 4793). The phenylhydrazone concentration in all the solvents investigated increased in the order of substituents 4-MeO < 4-Me < 3-Me ~ H ~ 4-Cl < 3-MeO < 2-Me < 3-Cl < 2-Cl < 2-MeO. It was noted that this was similar to the findings of Shingu (*Sci. Papers Inst. Phys. Chem. Res., Tokyo*, 1938, **35**, 78) for the tautomeric equilibria of the 1-arylazo-4-naphthols (II) in ethyl alcohol except that, in the latter series, *ortho*-substituents are responsible for unexpectedly small concentrations of the phenylhydrazone tautomer.

Burawoy and Chamberlain (*J.*, 1952, 2310), extending an earlier investigation by Morton and Stubbs (*J.*, 1940, 1347), found that, in absence of internal hydrogen bonding

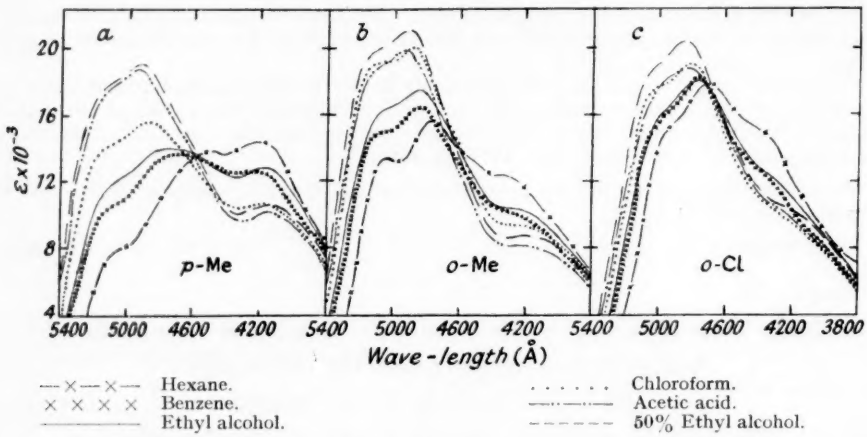
in the phenols and intramolecular steric effects in the methyl ethers, phenols absorb in hexane at shorter wave-lengths, but in ethyl alcohol and to a smaller degree in chloroform at longer wave-lengths, than the corresponding methyl ethers. This reversal of the normal effect of hydroxy- and methoxy-groups is due to the formation of hydrogen bonds by phenols with the latter solvents, the hydroxy-groups becoming more electron-repelling



(I) (II)

than the methoxy-groups in the methyl ethers. It was also pointed out that the same phenomenon would explain the fact that the dissociation constants of *m*- and *p*-methoxybenzoic and *m*-methoxycinnamic acid are higher than those of the corresponding hydroxy-derivatives in aqueous or alcoholic solution. Similarly, Bell and Bailey (*J.*, 1952, 1518), investigating the effect of substituents on the basicity of amines in chlorobenzene and

FIG. 1. 1-*Arylazo*-2-*naphthols*.



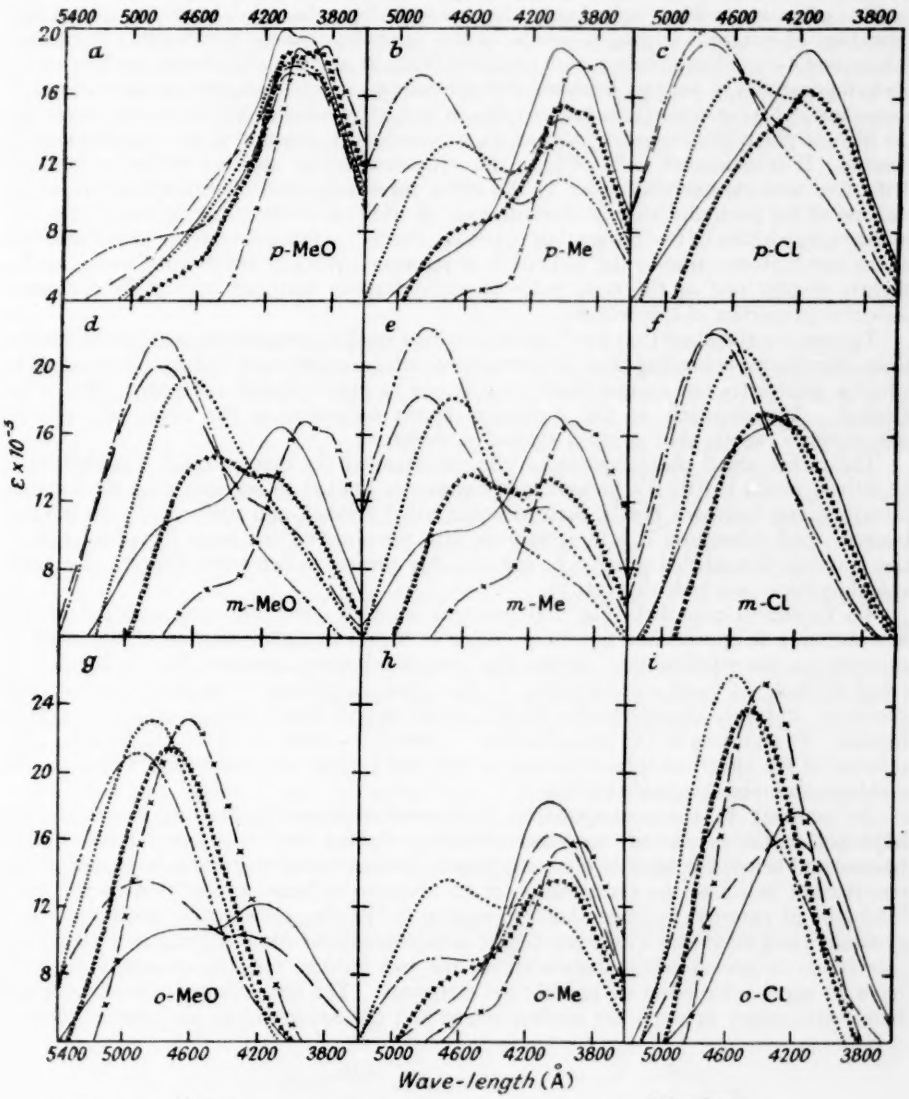
anisole, concluded that external hydrogen bonding is responsible for numerous anomalies of the dissociation constants observed in aqueous solution.

The effect of solvents on the tautomeric equilibria of 1-arylazo-2-naphthols is similar to that observed by Meyer (*Ber.*, 1912, **45**, 2843) on the keto-enol equilibria of ethyl acetoacetate and acetylacetone (Burawoy, Salem, and Thompson, *loc. cit.*). Since both tautomers in each of these systems are unable to form external hydrogen bonds, the concentration of the more polar ketonic structures increases in the order of solvents hexane < benzene ~ ethyl alcohol < chloroform < acetic acid < water, approximately in line with their increasing dielectric constant. It is important for the following discussion that this order is observed in all the 1-arylazo-2-naphthols investigated, including those substituted in the *ortho*-position. This is illustrated in Fig. 1 by the examples of 1-*p*-tolylazo-, 1-*o*-tolylazo-, and 1-*o*-chlorophenylazo-2-naphthol.

On the other hand, in the 4-arylazo-1-naphthol series the NH and the OH groups respectively of the tautomers are able to form hydrogen bonds with suitable solvents. We considered that the tautomers might be stabilised to a different degree by such bonds, and, in particular, that substituents in the *ortho*-position to the amino-group in the phenylhydrazone tautomers would inhibit sterically the formation of such bonds and be responsible for their observed anomalously low concentrations in ethyl alcohol. Investigation of the effect of solvents on the equilibria of 4-phenylazo-1-naphthol and its chloro-, methyl, and methoxy-derivatives confirms this view.

Figs. 2*a*—*f* show the spectra of the *meta*- and *para*-derivatives. The spectra of 4-phenylazo-1-naphthol itself are not reproduced, since they are almost identical with those of its *meta*-methyl derivative. The phenylhydrazone concentration increases in the order of

FIG. 2. 4-*Arylazo*-1-*naphthols*.



substituents 4-MeO < 4-Me < 4-Cl < H ~3-Me < 3-MeO < 3-Cl and in the order of solvents hexane < ethyl alcohol < benzene < chloroform ~50% ethyl alcohol < acetic acid. In contrast to the observations in the 1-arylazo-2-naphthol series, the phenylhydrazone concentration is considerably smaller in ethyl alcohol and 50% ethyl alcohol

than in benzene and acetic acid respectively. In the light of the following observations this is due to the formation of stronger hydrogen-bonds by the former solvents and the resulting greater stabilisation of the azo-tautomer, the hydrogen atom of the hydroxy-group forming stronger bonds than that of the NH group in the phenylhydrazone tautomer as expected.

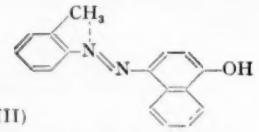
This effect is considerably enhanced by *ortho*-substituents, which sterically inhibit the formation of external hydrogen bonds in the phenylhydrazone tautomers. Both 4-*o*-chloro- and 4-*o*-methoxy-phenylazo-1-naphthol (Figs. 2*i* and *g*) exist almost exclusively as phenylhydrazones in hexane, benzene, and chloroform, and to a slightly smaller degree in acetic acid, whereas in ethyl alcohol and also in 50% ethyl alcohol which contains normally the highest phenylhydrazone concentration, a considerable amount of the azo-tautomer is present. It is estimated to be 50% in the aqueous-alcoholic solution of the *o*-methoxy-derivative and considerably more in the other three solutions. The surprisingly small increase of the phenylhydrazone concentration on addition of water to ethyl alcohol is due to the superposition of two strong, but opposing, effects : a relative increase of the stability of the azo-tautomer due to the formation of stronger hydrogen bonds with water, and a slightly greater one of the more polar phenylhydrazone tautomer due to the increased dielectric properties of this solvent.

The spectra also show that acetic acid contains a smaller phenylhydrazone concentration than chloroform, indicating that the former solvent forms stronger hydrogen bonds. The effect is similar to, but smaller than, that shown by ethyl alcohol and water (50% ethyl alcohol). The strength of the hydrogen bonds increases in the order of solvents chloroform < acetic acid < ethyl alcohol < water.

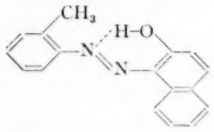
The rather small phenylhydrazone concentration of the *o*-substituted 4-phenylazo-1-naphthols which led to the present investigation is limited to solvents forming comparatively strong hydrogen bonds, such as water, ethyl alcohol, and acetic acid. In hexane, benzene, and chloroform it is in agreement with the observations made for all solvents in the 1-arylazo-2-naphthol series, *i.e.*, considerably greater in the *ortho*- than in the corresponding *para*- and *meta*-derivatives.

4-*o*-Tolylazo-1-naphthol (Fig. 2*h*) behaves similarly, but the concentration of the azo-tautomer is appreciably higher, resulting in a greater differentiation of the effect of solvents on the equilibrium. Again, the phenylhydrazone concentration is smallest in ethyl alcohol, no band corresponding to the phenylhydrazone tautomer being actually observed, and only slightly higher in 50% ethyl alcohol which is now similar to that in hexane. It increases in the order hexane < benzene < acetic acid < chloroform. The reversal of the effects of chloroform and acetic acid is even more pronounced than for the *o*-chloro- and *o*-methoxy-derivatives.

In contrast to the corresponding 1-arylazo-2-naphthol derivatives, 4-*o*-tolylazo-1-naphthol contains, not only in water and ethyl alcohol, but to a lesser degree also in hexane and benzene, a smaller phenylhydrazone concentration than its *meta*-isomer. This observation indicates the contribution of an alternative factor in addition to the steric inhibition of external hydrogen-bond formation in the phenylhydrazone tautomer. It is generally recognised that a different degree of intramolecular steric (repulsive or attractive) interaction involving *ortho*-substituents in the two entities forming an equilibrium can have an appreciable effect on equilibrium constants. The formation of a weak hydrogen bond (attraction) between the methyl group and the azo-group in the azo-tautomer of



(III)



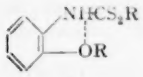
(IV)

4-*o*-tolylazo-1-naphthol (III) might be responsible for its increased stability. This would be prevented in the azo-tautomer of the isomeric 1-*o*-tolylazo-2-naphthol by the presence of the much stronger hydrogen bond involving the hydroxy-group (IV). The absence of

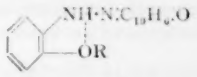
this anomaly in the *o*-chloro- and *o*-methoxy-derivatives respectively would also be accounted for.

Our observations as regards the effect of solvents on the tautomeric equilibria of the *ortho*-substituted 4-arylazo-1-naphthols are analogous to those just reported by Russell (*J. Amer. Chem. Soc.*, 1952, **74**, 2654) for the keto–enol equilibria of cyanodeoxybenzoin (V) and α-2-furoyl-α-phenylacetonitrile (VI), the concentrations of the enolic tautomers increasing in the order of solvents hexane < water < ethyl alcohol. This is not surprising, since in both series the enolic (phenolic), but not the ketonic, tautomers are able to form external hydrogen bonds with suitable solvents. This results in a superposition of the stabilising effect of external hydrogen-bond formation in the enolic (phenolic) tautomers on the normal, probably non-stoicheiometric dielectric effect of the solvents.

NC·CHPh·COR ⇌ NC·CPh:CR·OH
(V; R = Ph)
(VI; R = 2-furoyl)



(VII)



(VIII)

After submission of this paper, Burrows and Hunter (*J.*, 1952, 4118) reported that *o*-alkoxyphenyl-thion- and -dithio-carbamic and *o*-bromophenyldithiocarbamic esters are not (appreciably) associated in benzene, in contrast to the *o*-methyl derivatives (and all *m*- and *p*-isomers). They, therefore, suggest that this may be mainly due to the formation of internal hydrogen bonds (cf., *e.g.*, VII), rather than to steric influences. It is possible that the presence of such bonds will somewhat stabilise the phenylhydrazone tautomers of 4-*o*-methoxy- and 4-*o*-chlorophenylazo-1-naphthol (cf., *e.g.*, VIII), but, since these substances are, even in absence of such bonds, expected to exist almost exclusively as phenylhydrazones in solvents such as hexane and benzene, our observations cannot afford any evidence for this effect. We can also not exclude a partial contribution of this factor to the inhibition of external hydrogen-bond formation by these phenylhydrazones, but the analogous behaviour of 4-*o*-tolylazo-1-naphthol shows that steric influences are mainly responsible in this series.

Our investigation shows that the ability of molecules to form external hydrogen bonds with suitable solvents is an important factor determining equilibrium constants and, in particular, contributing to the qualitative anomalies often observed to be caused by *ortho*-substituents.

Experimental.—Spectra were determined with a Hilger Uvispek Photoelectric Spectrophotometer. The concentrations used varied between 0·000025M and 0·000125M, Beer's law being valid within these limits and the experimental error of this method. The light absorption of 4-*p*- and 4-*m*-chlorophenylazo-1-naphthol in hexane could not be measured owing to the low solubilities.

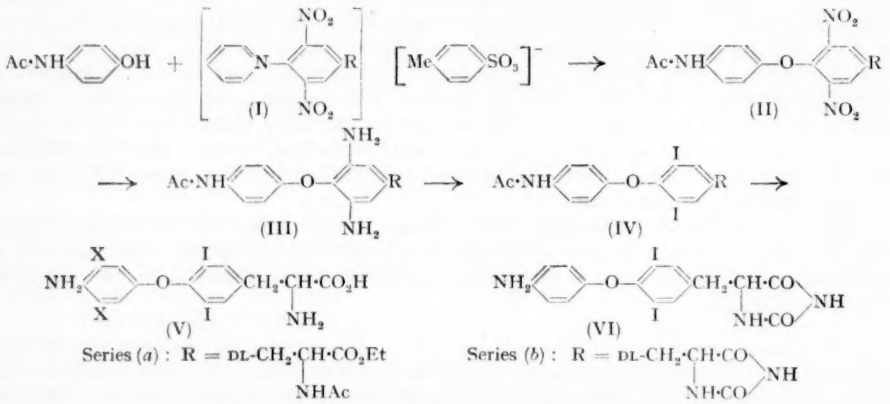
College of Technology, University of Manchester. [*Received, November 27th,* 1952.]

297. *The Synthesis of Thyroxine and Related Substances. Part XIII.* Some Further Analogues of Thyroxine.*

By J. H. Barnes, R. C. Cookson, G. T. Dickson, J. Elks, and V. D. Poole.

The preparation is described of the two "deoxythyroxines," 4-(3 : 5-di-iodophenoxy)-3 : 5-di-iodo-DL-phenylalanine (XV; R = R′ = H) and 4-(4-hydroxy-3 : 5-di-iodophenyl)-3 : 5-di-iodo-DL-phenylalanine (XXI), and of 3 : 5-di-iodo-3′ : 5′-dimethyl-DL-thyronine (XXVII). An attempt to prepare the 4′-amino-analogue of thyroxine failed, as 4-*p*-aminophenoxy-3 : 5-di-iodo-DL-phenylalanine (V; X = H) could not be iodinated. Some experiments leading towards the synthesis of the 3 : 5-dimethyl- and the 4′-mercapto-analogues of thyroxine are described. A new method of preparation of the known 2′ : 6′-di-iodothyronine is reported.

Several analogues of thyroxine have been reported that differ from the hormone in the nature of the side chain, in having the iodine atoms replaced by other halogen atoms, or in having the ether-oxygen atom replaced by sulphur. These minor variations have led so far to compounds with thyroxine-like activity rather than to thyroxine antagonists. It appears possible, nevertheless, that a close structural analogue might be found that, by competition with the hormone at the site of action, would act as an antagonist, and this paper describes the preparation of further analogues, of which two had the desired activity to a slight extent.



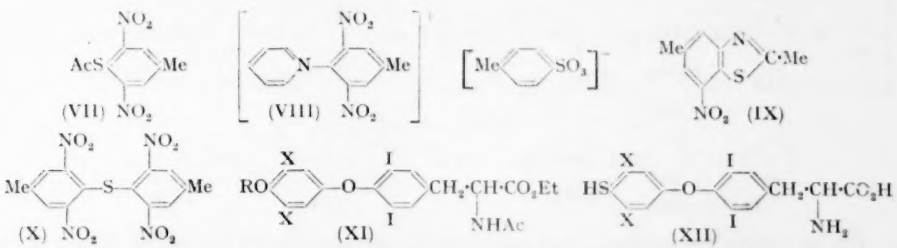
First, the preparation was attempted of compound (V; X = I) in which an amino-group replaces the phenolic hydroxyl of thyroxine. Reaction of aminophenols with quaternary toluene-*p*-sulphonates derived from 2 : 6-dinitrophenols is known to involve the amino- rather than the phenolic group (Cookson, Part XI, *J.*, 1953, 643). However, *p*-acetamidophenol reacted normally with (I*a*), prepared *in situ* from *N*-acetyl-3 : 5-dinitro-DL-tyrosine ethyl ester and toluene-*p*-sulphonyl chloride in pyridine, to yield the ether (II*a*). Catalytic reduction gave the diamine (III*a*), which could not be crystallised as such or in the form of various salts and acyl derivatives. Tetrazotisation of the crude diamine under anhydrous conditions, followed by treatment with sodium iodide, gave a high yield of the di-iododiphenyl ether (IV*a*), which was hydrolysed to the diamino-acid (V; X = H). Attempts to introduce iodine atoms *ortho* to the aromatic amino-group of this compound have all proved unavailing: iodine or iodine monochloride, under a variety of conditions, gave always either unchanged starting material or an intractable tar. Since the unprotected amino-acid grouping might be expected to be unstable in the more vigorous iodination conditions, several attempts were made to

* Part XII, *J.*, 1953, 764.

iodinate (IV*a*), in which all the functional groups are protected, but with no greater success.

It seemed desirable to attempt the iodination with a compound in which the aromatic amino-group was free, while the side-chain amino-acid group was protected in a stable derivative and to this end the hydantoin derivative (IV*b*) was prepared by reactions similar to those used in the preparation of (IV*a*). Hydrolysis with aqueous alcoholic hydrogen chloride gave the required amino-compound (VI), but here again treatment with iodine monochloride in acetic acid gave no crystalline product and the project was abandoned.

Of the methods considered for the preparation of the 4′-mercapto-analogue (XII; X = I) of thyroxine, those proceeding *via* (XII; X = H) were rejected, as it was considered that great difficulty would be encountered in the introduction of the 3′ : 5′-iodine atoms. Instead, routes to compounds of type (XII; X = NO_2) were investigated in the hope that the 3′ : 5′-nitro-groups would be replaceable by iodine atoms without undue complication.



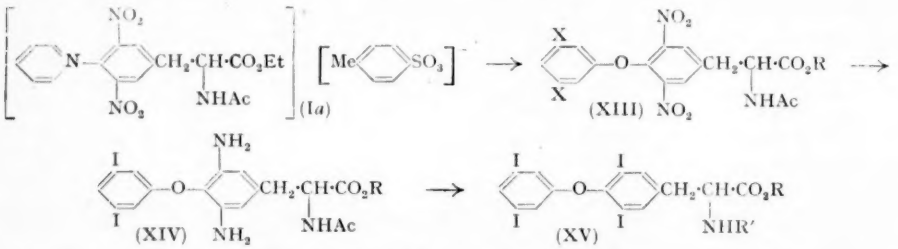
Chapman and Owen (*J.*, 1950, 579) have reported the preparation of alkyl thiolacetates by reaction of the corresponding alkyl toluene-*p*-sulphonate with potassium thioacetate. These authors showed that phenyl thiolacetate could not be prepared by this method, but it seemed probable that an aryl toluene-*p*-sulphonate suitably activated by nitro-groups might react as do the alkyl compounds. As an example 4-methyl-2 : 6-dinitrophenyl toluene-*p*-sulphonate was treated with potassium thioacetate under various conditions. With the thioacetate in excess in ethanol, the only product isolated was a compound of uncertain structure, but with one nitro-group reduced. When only one equivalent of potassium thioacetate was used, hydrolysis occurred and 4-hydroxy-3 : 5-dinitrotoluene was isolated. With acetone as solvent, however, and under carefully controlled conditions, the required 4-methyl-2 : 6-dinitrophenyl thiolacetate (VII) was obtained in fair yield.

In view of the ready reaction of 1-(2 : 6-dinitroaryl)pyridinium salts with phenols, the reaction of the quaternary salt (VIII) with thioacetic acid was investigated. When the latter was used in considerable excess, the product appeared to be 2 : 5-dimethyl-7-nitrobenzothiazole (IX), reaction of the required type having apparently occurred, followed by reduction of one of the nitro-groups and cyclisation. With only one equivalent of thioacetic acid and a short reaction time, some of the required compound (VII) could be isolated, but it was contaminated with the diphenyl sulphide (X), formed, presumably, by hydrolysis of (VII) and reaction with a further molecule of quaternary salt. With long reaction times the diphenyl sulphide was the only product isolated.

In order to apply these findings to the synthesis of (XII; X = NO_2), a suitable derivative of 3 : 5-di-iodo-3′ : 5′-dinitrothyronine was required. Nitration of *N*-acetyl-3 : 5-di-iodo-4-*p*-methoxyphenoxy-L-phenylalanine ethyl ester (XI; R = Me, X = H) (Part V, *J.*, 1949, 3424) in a mixture of sulphuric and acetic acids gave the 3′ : 5′-dinitro-derivative (XI; R = Me, X = NO_2). Alkyl aryl ethers containing two or more nitro-groups *ortho* or *para* to the ether linkage are known to be smoothly demethylated by pyridine (Kohn and Grauer, *Monatsh.*, 1913, **34**, 1751; Kohn and Loff, *ibid.*, 1924, **45**, 605; Cahn, *J.*, 1931, 630, 1121), and the required thyronine derivative (XI; R = H, X = NO_2) was obtained from its methyl ether in this way. Both the toluene-*p*-sulphonate, which could not be obtained crystalline, and the quaternary salt derived from it by treatment with pyridine were prepared, and these compounds were treated with potassium thio-

acetate and thioacetic acid respectively. Unfortunately, the conditions that led successfully to the thiophenol derivative in the model experiments gave only gums, from which no pure product could be isolated, and the investigation was carried no further.

Preparation of the " deoxythyroxine " (XV; R = R′ = H) was first attempted *via* the tetranitro-compound (XIII; R = Et, X = NO_2), which was prepared in the usual way from the quaternary salt (I*a*) and 3 : 5-dinitrophenol. The reaction was sluggish, and even after 66 hr. the yield was unusually low. In the presence of palladised charcoal, (XIII; R = Et, X = NO_2) absorbed hydrogen sufficient to reduce all four nitro-groups, but the product was very unstable and could not be crystallised or converted into a crystalline derivative. In spite of efforts to prevent aerial oxidation while the crude material was treated successively with nitrosylsulphuric acid and sodium iodide, none of the required tetra-iodo-compound (XV; R = Et, R′ = Ac) could be isolated from the tarry product.



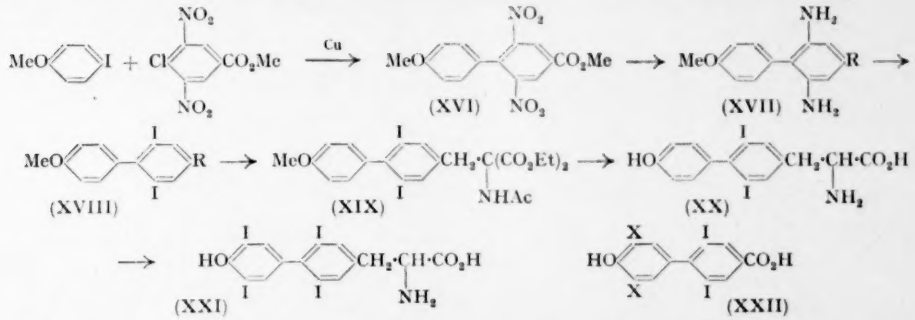
For an alternative method, involving stepwise introduction of the iodine atoms, 3 : 5-di-iodophenol was required, but neither of the methods of preparation described in the literature proved satisfactory (Willgerodt and Arnold, *Ber.*, 1901, **34**, 3343; Brenans, *Compt. rend.*, 1903, **136**, 236; *Bull. Soc. chim.*, 1903, **29**, 227; Hodgson and Wignall, *J.*, 1926, 2077). However, a simple and convenient method was found in the catalytic hydrogenation of 3 : 5-dinitroanisole, replacement of the resulting amino-groups by iodine, and demethylation with hydriodic acid.

Treatment of the quaternary salt (I*a*) with 3 : 5-di-iodophenol gave a satisfactory yield of *N*-acetyl-4-(3 : 5-di-iodophenoxy)-3 : 5-dinitro-DL-phenylalanine ethyl ester (XIII; X = I, R = Et). The nitro-groups in this compound could not be reduced catalytically without simultaneous removal of the iodine atoms, and several mild chemical reducing agents failed to affect the material or the corresponding acid. The required product was finally obtained by treatment of (XIII; X = I, R = Et) with iron powder in hydrochloric–acetic acids. Replacement of the amino-groups by iodine in the usual way, and hydrolysis, gave the amino-acid (XV; R = R′ = H).

For the preparation of the diphenyl derivative (XXI), a " deoxythyroxine " isomeric with (XV; R = R′ = H), *p*-iodoanisole and methyl 4-chloro-3 : 5-dinitrobenzoate were treated at 240° with copper bronze, to give methyl 4′-methoxy-2 : 6-dinitrodiphenyl-4-carboxylate (XVI) in *ca.* 50% yield. This result was not unexpected since, although the yields of unsymmetrical diaryls produced by the Ullmann method tend to be low owing to competing formation of the symmetrical compounds, several examples have been described of satisfactory reaction when one of the components has two bulky groups *ortho* to the halogen atom (Lesslie and Turner, *J.*, 1930, 1758; 1931, 1188; Rule and Smith, *J.*, 1937, 1096). A minor by-product of the reaction was methyl 3 : 5-dinitrobenzoate.

Catalytic hydrogenation of (XVI) gave the diamine (XVII; R = CO_2Me), which was converted *via* the tetrazonium salt, prepared under the usual anhydrous conditions, into the di-iodo-ester (XVIII; R = CO_2Me), from which (XXII; X = I) was prepared by standard methods. Although lithium aluminium hydride is known to be capable of reducing aromatic iodo-compounds (Trevoy and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 1675), it was hoped that selective reduction of the carbomethoxy-group of (XVIII; R = CO_2Me) might be possible under controlled conditions. Treatment of the ester with an

equimolecular quantity of lithium aluminium hydride at 0° gave a gum that, after acetylation, yielded crystalline (XVIII; R = CH_2·OAc) in only 33% of the theoretical amount. Reduction of the quantity of reducing agent left some ester unchanged, but had no effect on the net yield of the required material. Analysis of the crude products of such reductions showed that partial loss of iodine was occurring. Nevertheless, the crude alcohol (XVIII; R = CH_2·OH) obtained from a reduction was treated with thionyl chloride and the chloromethyl compound (XVIII; R = CH_2Cl), again without purification, was condensed with sodio-acetamidomalonic ester to give a rather poor yield of (XIX). The malonic ester (XIX) was stripped of its protecting groups by means of a mixture of hydriodic and acetic acids. Iodination of the resulting amino-acid (XX) gave the required 4-(4-hydroxy-3 : 5-di-iodophenyl)-3 : 5-di-iodo-DL-phenylalanine (XXI).



Because of the unsatisfactory reduction stage in the synthesis described above, some experiments were carried out on an alternative route which avoided the necessity for selective reduction. The di-amino-ester (XVII; R = CO_2Me) was smoothly reduced with excess of lithium aluminium hydride to the alcohol (XVII; R = CH_2·OH). Tetrazotisation of this compound with nitrosylsulphuric acid in acetic acid followed by decomposition with iodide gave a fair yield of (XVIII; R = CH_2·OAc), acetylation of the hydroxyl group having occurred during tetrazotisation. Alkaline hydrolysis of this acetate gave the pure alcohol (XVIII; R = CH_2·OH).

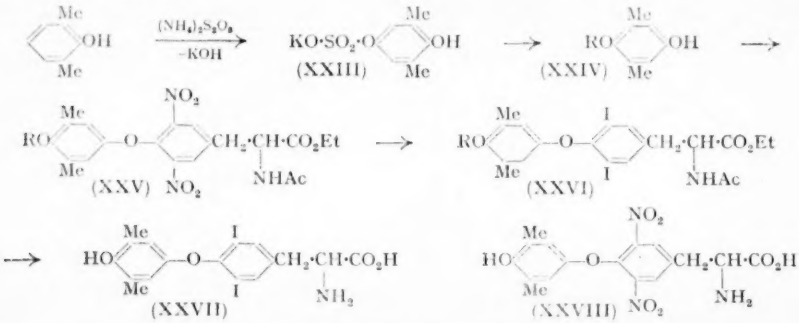
Substitution of the methyl groups of riboflavin by chlorine atoms leads to a compound that antagonises the action of the vitamin (Kuhn, Weygand, and Möller, *Ber.*, **1943**, **76**, 1044). This may well be due to the similarity in the dimensions of the methyl group and the chlorine atom, but we have nevertheless investigated the preparation of compounds in which some or all of the iodine atoms of thyroxine are replaced by methyl groups, in the hope that an antagonist might result.

2 : 6-Dimethylquinol was prepared from 2 : 6-dimethylphenol by oxidation with ammonium persulphate and hydrolysis of the sulphate (XXIII) so formed (Baker and Brown, *J.*, 1948, 2303). Contrary to the experience of these authors we find ammonium persulphate to be preferable to the potassium salt, which gave rather lower yields and was inconveniently insoluble.

Reaction of 2 : 6-dimethylquinol with the quaternary salt (I*a*) gave a mixture that, after chromatography and repeated recrystallisation, yielded a small quantity of the required diphenyl ether (XXV; R = H). It seemed probable that this compound, formed by reaction of the unhindered hydroxyl group of 2 : 6-dimethylquinol, would be obtained in preference to the isomeric *N*-acetyl-4-(4-hydroxy-2 : 6-dimethylphenoxy)-3 : 5-dinitro-DL-phenylalanine ethyl ester, and evidence that the compound isolated was in fact (XXV; R = H) was provided by comparison of the free amino-acid (XXVIII), obtained from it by hydrolysis, with an authentic specimen prepared by the method described below. The amino-acid melted with decomposition, and the mixed melting point test was not, therefore, wholly satisfactory, but further evidence was provided by the fact that the compound gave no colour when treated with benzene- or *p*-nitrobenzene-diazonium chloride, indicating the absence of an unsubstituted position

ortho to the phenolic hydroxyl. The presence of the isomeric compound among the products of the above reaction is certainly not excluded, and its presence may, indeed, account for the difficulty encountered in isolating (XXV; R = H) in a pure state.

In view of the unsatisfactory nature of the above reaction, the 1-hydroxy-group of 2 : 6-dimethylquinol was then blocked before reaction with the quaternary salt. Attempts to acetylate or benzoylate the free hydroxy-group of (XXIII) led, after removal of the sulphate ester grouping, only to some 2 : 6-dimethylquinol. Treatment with methyl sulphate (Baker and Brown, *loc. cit.*) and acid hydrolysis gave a moderate yield of 4-methoxy-3 : 5-dimethylphenol (XXIV; R = Me); benzyl chloride gave the corresponding benzyl ether (XXIV; R = CH_2Ph), but in only 18% yield. Comparison of the last result with the quantitative yield obtained by benzylation of the isomeric potassium 4-hydroxy-2 : 6-dimethylphenyl sulphate (Baker and Brown, *loc. cit.*) shows the effect of the two *o*-methyl groups.



The quaternary salt (I*a*) reacted with (XXIV; R = Me) to give the diphenyl ether (XXV; R = Me) and with (XXIV; R = CH_2Ph) to give (XXV; R = CH_2Ph). Earlier experiments (Part VIII, *J.*, 1951, 2467) have shown that 4'-methoxy-2 : 6-dinitrodiphenyl ethers are not readily demethylated, but it was found that the more labile benzyloxy-group of (XXV; R = CH_2Ph) could be cleaved by boiling aqueous alcoholic hydrochloric acid, to give 3' : 5'-dimethyl-3 : 5-dinitro-DL-thyronine (XXVIII).

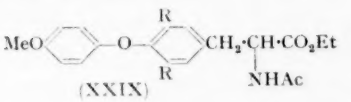
The methoxy-compound (XXV; R = Me) was reduced catalytically, and the diamine, without isolation, was converted into the di-iodo-compound (XXVI) in the usual way. Treatment of this compound with hydriodic acid gave the required 3 : 5-di-iodo-3' : 5'-dimethyl-DL-thyronine (XXVII), though here again the effect of the methyl groups was shown by the sluggishness of the reaction.*

The 3 : 5-dimethyl analogue of thyroxine proved, as expected, to be much less accessible than the isomer already described. However, although the required compound was not synthesised, we record here the results of preliminary experiments for the light they throw on the preparation of 2 : 6-dimethyldiphenyl ethers.

The ease with which 2 : 6-di-iododiphenyl ethers can be prepared made these appear attractive intermediates for the preparation of the dimethyl compounds. The first method examined for the replacement of iodine atoms by methyl groups proceeded *via* the dinitrile. *N*-Acetyl-3 : 5-dicyano-4-*p*-methoxyphenoxy-L-phenylalanine ethyl ester (XXIX; R = CN) was readily prepared by treatment of the 3 : 5-di-iodo-compound (XXIX; R = I) (Part V, *J.*, 1949, 3424) with cuprous cyanide in boiling pyridine. An attempt to prepare the same compound from (XXIX; R = NH_2) (Part V, *loc. cit.*) by tetrazotisation, followed by treatment with sodium cuprocyanide, was unsuccessful. It was hoped that the cyano-groups could be reduced to aminomethyl groups, which should then be convertible into methyl groups, but several attempts to reduce (XXIX; R = CN) catalytically failed to produce a pure product. In view of the very smooth reaction of (XXIX; R = I) with cuprous cyanide, it is surprising that several rather similar

* Since this manuscript was prepared, Bruice, Kharasch, and Winzler (*J. Org. Chem.*, 1953, **18**, 83) have described the preparation of the L-isomer of (XXVII) by a similar method.

compounds, namely, L-thyroxine, *N*-acetyl-L-thyroxine, *ON*-diacetyl-3 : 5-di-iodo-L-tyrosine ethyl ester, and *N*-acetyl-3 : 5-di-iodo-*O*-methyl-L-tyrosine ethyl ester, either failed to react under similar conditions or yielded products from which no pure material could be isolated.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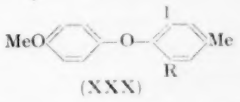
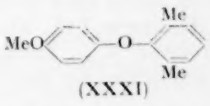
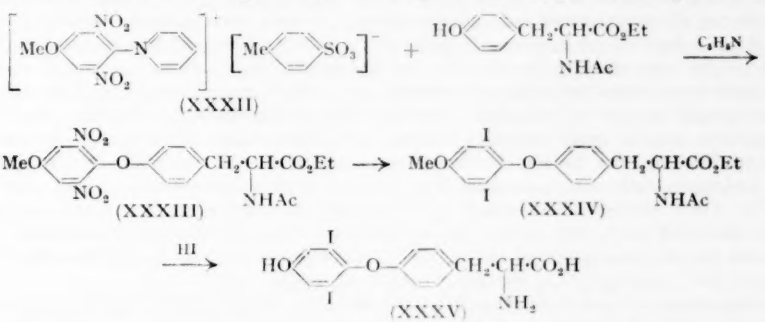

(XXX)


(XXXI)

Another method considered for converting 2 : 6-di-iododiphenyl ethers into the dimethyl compounds involved methylation of the Grignard compound derived from the former. However, carboxylation of 3 : 5-di-iodo-4′-methoxy-4-methyldiphenyl ether (XXX; R = I) after treatment with magnesium and some methyl iodide gave an iodo-acid (XXX; R = CO_2H), indicating that only one iodine atom had reacted.

It was expected that the conditions required for reaction of a 2 : 6-dimethylphenol with an unactivated aromatic halide would be so vigorous that, if a thyroxine analogue were to be prepared, the alanine side-chain would have to be built up subsequently from a simple, stable group such as carbethoxy. In accordance with this, 2 : 6-dimethylphenol, itself, could not be made to react with bromobenzene in the Ullmann reaction, but the more reactive halogen of *p*-iodoanisole permitted reaction, and a moderate yield of 4′-methoxy-2 : 6-dimethyldiphenyl ether (XXXI) resulted after prolonged treatment with 2 : 6-dimethylphenol in the presence of potassium carbonate and copper bronze at 220—240°.* This experiment demonstrates that such an approach to the 3 : 5-dimethyl analogue of thyroxine is feasible, but we were unable to carry the investigation beyond this point.

Finally, we describe the preparation of the known 2′ : 6′-di-iodothyronine (XXXV) by a new route. The DL-form of this amino-acid was described by Niemann and McCasland (*J. Amer. Chem. Soc.*, **1944**, **66**, **1870**). The essential stages of their synthesis were the reaction of 3 : 4 : 5-tri-iodo-nitrobenzene with *N*-benzoyl-DL-tyrosine ethyl ester and replacement of the 4′-nitro-group in the resulting diphenyl ether by a hydroxy-group, *via* the amino- and diazonium compounds. Cortell (*J. Clin. Endocrinol.*, **1949**, **9**, 955) reported that (XXXV) antagonises the effect of thyroxine in thiouracil-treated rats, as shown by the thyroid weight. We have now prepared both the L- and the DL-form of the compound in order to investigate their activity in the oxygen-consumption test. The


(XXXII)

(XXXIII)

(XXXIV)

(XXXV)

synthesis, an adaptation of our normal method for preparing di-iododiphenyl ethers, is illustrated by the formulæ (XXXII)—(XXXV). *N*-Acetyl-L-tyrosine ethyl ester was used as starting material, and the DL-acid (XXXV) was prepared by racemising the acetamido-ester (XXXIV) with sodium methoxide and treating the product with hydriodic acid. The melting point of our material was substantially higher than that reported by Niemann and McCasland (*loc. cit.*).

* Bruice, Kharasch, and Winzler (*loc. cit.*) have described the preparation of 4′-methoxy-2 : 6 : 3′ : 5′-tetramethyldiphenyl ether by heating a mixture of 4-bromo-2 : 6-dimethylanisole, 2 : 6-dimethylphenol, potassium hydroxide, and copper bronze at 235° for 3 hr.

Biological Results.—The various thyroxine analogues and certain of the intermediates reported in this paper have been examined for anti-thyroid activity by the method outlined in Part XII. All were inactive with the exception of compound (XXII; X = H) and DL-2′ : 6′-di-iodothyronine (XXXV), both of which showed slight activity. The tests were partly done in the pharmacological laboratories of the Research Division of Glaxo Laboratories Ltd., where they were under the direction of Mr. E. G. Tomich, and partly by Professor N. F. Maclagan and his colleagues at Westminster Medical School, to whom we are indebted for their assistance.

Experimental

4-p-*Acetamidophenoxy*-N-*acetyl*-3 : 5-*dinitro*-DL-*phenylalanine Ethyl Ester* (II*a*).—*N*-Acetyl-3 : 5-dinitro-DL-tyrosine ethyl ester (Part VIII, *J.*, 1951, 2467) (16 g.) and toluene-*p*-sulphonyl chloride (9·8 g.) in pyridine (70 c.c.) were kept at 110° for 1 hr. *p*-Acetamidophenol (21 g.) was added and the mixture boiled gently under reflux for 2 hr. The cooled solution was poured into a large volume of dilute hydrochloric acid, from which the product was extracted with two portions of ethyl acetate. After being washed with very dilute sodium hydroxide solution and water the solution was evaporated to dryness. The residual oil crystallised when seeded. However, recrystallisation was difficult and did not give a sharply melting product. The material was, therefore, redissolved in dry ethyl acetate and passed down a column of activated alumina. Recrystallisation of the most easily eluted fractions from alcohol gave the *diphenyl ether* (13 g., 58%), m. p. 175—177°. Repeated recrystallisation from alcohol or aqueous methanol yielded pale yellow needles, m. p. 178° (Found: C, 53·2; H, 4·8. $C_{21}H_{22}O_9N_4$ requires C, 53·15; H, 4·7%).

When this diacetamido-ester was boiled in aqueous-alcoholic hydrochloric acid for 2 hr., the *diamino-acid dihydrochloride* separated on cooling. After crystallisation from fairly concentrated hydrochloric acid it formed almost colourless needles, beginning to blacken at about 250° (Found: C, 41·2; H, 3·8; N, 12·75. $C_{15}H_{14}O_7N_4,2HCl$ requires C, 41·4; H, 3·7; N, 12·9%).

4-p-*Acetamidophenoxy*-N-*acetyl*-3 : 5-*di-iodo*-DL-*phenylalanine Ethyl Ester* (IV*a*).—The dinitro-compound (8·1 g.) in alcohol (220 c.c.) rapidly absorbed hydrogen when stirred under hydrogen at 80 atm. in the presence of palladised charcoal (10%; 1 g.). Filtration through kieselguhr and distillation of the alcohol at reduced pressure in an atmosphere of carbon dioxide left the 3 : 5-diamine as an almost colourless gum.

The gum, dissolved in acetic acid (23 c.c.), was slowly added to sulphuric acid (12 c.c.) cooled below −5°. This solution was added during 45 min. to a solution of sodium nitrite (2·8 g.) in a mixture of sulphuric acid (30 c.c.) and acetic acid (50 c.c.), well stirred at <0°. After another hr. at 0° the mixture was added during 15 min. to a stirred solution of sodium iodide (18 g.), iodine (15 g.) and urea (1 g.) in water (300 c.c.) and chloroform (100 c.c.) at 35°. After an hr. the chloroform was separated and the lower, black, viscous layer and the upper, aqueous layer were extracted with more chloroform. However, evaporation of the chloroform left only a small amount of material. The lower layer was, therefore, shaken with sodium iodide solution, sodium metabisulphite solution, and then water. The last of the iodine was removed by dissolving the material in alcohol and treating the solution with sulphur dioxide and sodium hydrogen carbonate. Pouring the solution into water gave a sticky gum which crystallised when warmed and seeded. The product was ground under water, washed, and dried; it then had m. p. 211—216°. Recrystallisation from alcohol and twice from aqueous dioxan gave the *di-iodo*-compound (5·0 g., 46%) as colourless needles, m. p. 224—225° (Found: C, 39·5; H, 3·5. $C_{21}H_{22}O_5N_2I_2$ requires C, 39·6; H, 3·5%).

4-p-*Aminophenoxy*-3 : 5-*di-iodo*-DL-*phenylalanine* (V; X = H).—The above diacetamido-ester (1 g.), alcohol (6 c.c.), water (3·5 c.c.), and concentrated hydrochloric acid (3·5 c.c.) were boiled for 3 hr. Concentrated hydrochloric acid (1 c.c.) was added and the needles of the *diamino-acid dihydrochloride* (0·8 g.; 85%) which had separated were filtered off and washed with dilute hydrochloric acid. Recrystallisation from 2N-hydrochloric acid yielded fine colourless needles, beginning to decompose at 250° (Found: C, 30·3; H, 3·0. $C_{15}H_{14}O_3N_2I_2,2HCl$ requires C, 30·15; H, 2·7%).

DL-5-(4-p-*Acetamidophenoxy*-3 : 5-*dinitrobenzyl*)*hydantoin* (II*b*).—DL-5-(4-Hydroxy-3 : 5-dinitrobenzyl)hydantoin (Part III, *J.*, 1949, S 199) (10 g.) and toluene-*p*-sulphonyl chloride (6·5 g., 1 mol.) in pyridine (40 c.c.) were heated at 100° for 45 min. After the addition of *p*-acetamidophenol (15 g., 3 mol.) to the cooled solution the mixture was reheated for 2 hr.,

cooled, and poured into dilute hydrochloric acid. The solid was filtered off, washed, dissolved in the minimum amount of dilute sodium hydroxide solution, and, after filtration of the solution, reprecipitated with dilute hydrochloric acid. Recrystallisation from acetic acid (charcoal) produced the pure *ether* (8·6 g., 60%) as a yellow powder, melting with effervescence at 275° (Found: C, 50·4; H, 3·6; N, 16·4. $C_{18}H_{15}O_8N_5$ requires C, 50·35; H, 3·5; N, 16·3%).

DL-5-(4-p-*Acetamidophenoxy*-3 : 5-*di-iodobenzyl*)*hydantoin* (IV*b*).—The foregoing dinitro-compound (1 g.) was hydrogenated in acetic acid (50 c.c.) at ordinary temperature and pressure in the presence of palladised charcoal (0·5 g.). The theoretical amount of hydrogen was taken up in 6 hr. The solution, after removal of the catalyst, was added to sulphuric acid (30 c.c.) kept at about 10°. A solution of sodium nitrite (0·4 g.) in sulphuric acid (50 c.c.) and acetic acid (50 c.c.) was cooled to −5° and stirred whilst the diamine solution was added dropwise during 30 min. The mixture was then stirred at 0° for 1½ hr. more and added dropwise during 10 min. to a stirred solution of iodine (5 g.) and sodium iodide (5 g.) in water (200 c.c.). The mixture was kept for 2 hr. and the black solid was filtered off and treated with sodium meta-bisulphite solution to remove free iodine, a buff-coloured solid resulting. After drying, this was chromatographed in acetone (100 c.c.) on alumina. A mixture of acetone (90%), methanol (5%), and acetic acid (5%) eluted a solid which after crystallisation from a little acetic acid gave the *di-iodo*-compound (0·86 g., 57%) as pale buff-coloured crystals, m. p. 290° after sintering at 160° (Found: N, 6·5; I, 38·8. $C_{18}H_{15}O_4N_3I_2,CH_3{\cdot}CO_2H$ requires N, 6·5; I, 39·0%).

DL-5-(4-p-*Aminophenoxy*-3 : 5-*di-iodobenzyl*)*hydantoin* (VI).—A solution of the *N*-acetyl derivative (3·3 g.) in ethanol (50 c.c.) and concentrated hydrochloric acid (10 c.c.) was boiled under reflux for 45 min. After cooling, the solid was filtered off and dissolved in hot water (100 c.c.). The solution was decolorised with charcoal, filtered, and brought to pH 5 by addition of sodium acetate solution. The *amine* was precipitated as a pale buff-coloured powder, m. p. 261—264°. Crystallisation from aqueous ethanol gave almost colourless crystals (1·7 g., 59%), m. p. 210° (Found: C, 35·2; H, 3·0; N, 7·3; I, 44·3. $C_{16}H_{13}O_3N_3I_2,\frac{1}{2}EtOH$ requires C, 35·7; H, 2·8; N, 7·3; I, 44·4%).

4-*Methyl*-2 : 6-*dinitrophenyl Thiolacetate* (VII).—3 : 5-Dinitro-*p*-tolyl toluene-*p*-sulphonate (1 g.) was dissolved in boiling acetone (25 c.c.), potassium thioacetate (0·32 g.) was then added, and refluxing continued for a few min., until there was no further separation of solid. On dilution of the cooled mixture with water yellow crystals slowly separated. After an hour this material was collected and crystallised from light petroleum (b. p. 80—100°). The *thiolacetate* (350 mg., 48%) separated as pale yellow plates, m. p. 132—134° (Found: C, 42·2; H, 3·2; N, 11·0; S, 12·3. $C_9H_8O_5N_2S$ requires C, 42·2; H, 3·2; N, 11·0; S, 12·5%).

Reaction between N-(4-*Methyl*-2 : 6-*dinitrophenyl*)*pyridinium Toluene*-p-*sulphonate and Excess of Thioacetic Acid.*—The pyridinium salt (Part II, *J.*, 1949, S 190) (1·05 g.), thioacetic acid (0·56 c.c., 3 mols.), dry chloroform (10 c.c.), and dry pyridine (3 c.c.) were refluxed together for 12 hr. Evaporation to dryness under diminished pressure left an orange-red oil which solidified. This material was dissolved in ethanol (10 c.c.) and filtered from sulphur, and the clear solution diluted with water (50 c.c.). The solid was collected, dried, and crystallised from aqueous ethanol from which 2 : 5-*dimethyl*-7-*nitrobenzothiazole* (0·22 g.) separated as faintly yellow needles, m. p. 136—138° (Found: C, 52·1; H, 4·0; S, 15·2. $C_9H_8O_2N_2S$ requires C, 51·9; H, 3·9; S, 15·4%).

The material was insoluble in dilute hydrochloric acid, but dissolved in the concentrated acid from which it was precipitated unchanged by dilution with water.

Reaction between N-(4-*Methyl*-2 : 6-*dinitrophenyl*)*pyridinium Toluene*-p-*sulphonate and One Molecular Proportion of Thioacetic Acid.*—(*a*) A mixture of the pyridinium salt (1·25 g.), thio-acetic acid (0·21 c.c., 1 mol.), dry chloroform (10 c.c.), and dry pyridine (3 c.c.) was refluxed for 2 hr. A yellow solid separated during this time. The mixture was evaporated to smaller bulk, diluted with water, and extracted with chloroform (3 × 40 c.c.). Evaporation left a yellow solid (0·13 g., 11%) which was washed with a little ethanol and dried (m. p. 272—275°). Crystallisation from chloroform–light petroleum (b. p. 60—80°) gave *di*-(4-*methyl*-2 : 6-*dinitro-phenyl*) *sulphide* (X) as a yellow solid, m. p. 274—275° (Found: C, 43·0; H, 2·9; N, 14·4; S, 8·2. $C_{14}H_{10}O_8N_4S$ requires C, 42·6; H, 2·6; N, 14·2; S, 8·1%).

When the reaction was carried out in dry pyridine for 48 hr. at room temperature, a similar yield of the same product was obtained.

(*b*) The pyridinium salt (1·1 g.) and thioacetic acid (0·185 c.c., 1 mol.) in dry chloroform (25 c.c.) were heated to boiling, and then dry pyridine (1 c.c.) was added. All the solid rapidly dissolved and the solution was then evaporated to dryness under reduced pressure. The

residual oil solidified on trituration with water. The dried solid was extracted with light petroleum (b. p. 80—100°), and the extract, on cooling, gave 4-methyl-2 : 6-dinitrophenyl thiolacetate (120 mg.), m. p. 121—124°. Further crystallisation raised the m. p. to 132—134°.

The solid left from the extraction crystallised from chloroform–light petroleum, giving di-(4-methyl-2 : 6-dinitrophenyl) sulphide (130 mg.), m. p. 264—266°.

N-*Acetyl*-3 : 5-*di-iodo*-4-(4-*methoxy*-3 : 5-*dinitrophenoxy*)-L-*phenylalanine Ethyl Ester* (XI; R = Me, X = NO_2).—A suspension of *N*-acetyl-3 : 5-di-iodo-4-*p*-methoxyphenoxy-L-phenylalanine ethyl ester (Part V, *J.*, 1949, 3424) (5 g.) in glacial acetic acid (10 c.c.) was treated slowly below 25° with concentrated sulphuric acid (20 c.c.). The resulting clear solution was stirred and kept between 5° and 10° while nitric acid (*d* 1·42; 1·2 c.c.) was added dropwise. When addition was complete, the mixture was stirred for a further 20 min. and then poured on crushed ice. The solid was washed with water, dried, and crystallised from aqueous ethanol from which the *dinitro*-compound (3·8 g., 66%) separated as aggregates of soft needles, m. p. 167—168°, $[\alpha]_D^{22}$ +19·5° (*c*, 1·98 in dioxan) (Found: C, 34·5; H, 2·7; N, 6·1; I, 36·5. $C_{20}H_{19}O_9N_3I_2$ requires C, 34·4; H, 2·7; N, 6·0; I, 36·3%).

N-*Acetyl*-3 : 5-*di-iodo*-3′ : 5′-*dinitro*-L-*thyronine Ethyl Ester* (XI; R = H, X = NO_2).—A solution of the foregoing ether (3·7 g.) in pyridine (40 c.c.) was refluxed for 1 hr., during which a deep red colour developed. After cooling, dilution with dry ether precipitated a red solid which appeared to be deliquescent. The liquid phase was decanted and the residue washed twice with dry ether. 2N-Sulphuric acid (100 c.c.) was then added and the mixture warmed gently to remove traces of ether. The solid was ground under the acid until all the red product had disappeared. The bright yellow material remaining was collected, washed with water, dried, and crystallised from aqueous dioxan, from which N-*acetyl*-3 : 5-*di-iodo*-3′ : 5′-*dinitro*-L-*thyronine ethyl ester* (2·1 g., 51%) separated as yellow needles. The compound, which contained a molecule of dioxan of crystallisation, melted first at 115°, resolidified, and remelted at 161—163°, $[\alpha]_D^{19}$ +17·6° (*c*, 1·06 in dioxan) (Found: C, 35·5; H, 3·3; N, 5·4; I, 32·9. $C_{19}H_{17}O_9N_{23}I,C_4H_8O_2$ requires C, 35·8; H, 3·3; N, 5·4; I, 32·8%).

3 : 5-*Di-iodo*-3′ : 5′-*dinitro*-L-*thyronine*.—The above acetamido-ester (1 g.), concentrated hydrochloric acid (5 c.c.), and acetic acid (5 c.c.) were refluxed for 2 hr. On cooling, a yellow solid separated and this was collected and dried. It was purified by dissolving it in acetic acid containing a little hydrochloric acid, and carefully adding water. The *amino-acid* (0·6 g., 75%) separated as yellow needles, m. p. 270° (decomp.) (Found: C, 29·6; H, 2·0; I, 42·0. $C_{15}H_{11}O_8N_3I_2$ requires C, 29·3; H, 1·8; I, 41·3%).

N-*Acetyl*-4-(3 : 5-*dinitro*-4-*toluene*-p-*sulphonyloxyphenoxy*)-3 : 5-*di-iodo*-L-*phenylalanine Ethyl Ester* (XI; R = *p*-Me·C_6H_4·SO_2, X = NO_2).—*N*-Acetyl-3 : 5-di-iodo-3′ : 5′-dinitro-L-thyronine ethyl ester (1·0 g.) and toluene-*p*-sulphonyl chloride (0·28 g.) were dissolved in acetone (10 c.c.), and N-sodium hydroxide (1·46 c.c.) was added slowly with stirring. After 2 hr., the bulk of the acetone was evaporated off under diminished pressure and the residue diluted with water. The oil first formed solidified when scratched, and this solid was ground with water, collected, and dried. The toluene-*p*-sulphonate was a pale yellow solid, m. p. *ca.* 85°, which could not be crystallised.

N-*Acetyl*-4-(3 : 5-*dinitrophenoxy*)-3 : 5-*dinitro*-DL-*phenylalanine Ethyl Ester* (XIII; X = NO_2, R = Et).—A solution of *N*-acetyl-3 : 5-dinitro-DL-tyrosine ethyl ester (10 g.) and toluene-*p*-sulphonyl chloride (6·25 g.) in acetone (60 c.c.) was stirred while 2N-sodium hydroxide (15 c.c.) was added dropwise during 1 hr. After a further 2 hr. stirring the mixture was evaporated nearly to dryness and the residue dissolved in benzene (125 c.c.). The solution was washed successively with water, N-sodium hydroxide, and water, dried, and evaporated to about 10 c.c. Pyridine (6·8 c.c.) was then added and the solution refluxed for 30 min. during which the quaternary salt separated as a sticky gum, from which the benzene was decanted. The gum was dissolved in a mixture of chloroform (50 c.c.) and pyridine (15 c.c.) and, after the addition of 3 : 5-dinitrophenol (17 g.), the solution refluxed for 66 hr. After dilution with chloroform (500 c.c.) the solution was washed successively with N-hydrochloric acid, water, N-sodium hydroxide, and water. Evaporation of the dried solution left a white solid which crystallised from ethanol, giving the *tetranitro*-compound (6·8 g., 45%) as needles, m. p. 183—184° (Found: C, 45·2; H, 3·6; N, 13·5. $C_{19}H_{17}O_{12}N_5$ requires C, 45·0; H, 3·4; N, 13·8%).

3 : 5-*Di-iodoanisole*.—3 : 5-Dinitroanisole (*Org. Synth.*, Coll. Vol. I, 2nd Edn., p. 219) (16 g.) in glacial acetic acid (300 c.c.) was hydrogenated at ordinary temperature and pressure in the presence of Adams's catalyst. Subsequent operations were conducted in an atmosphere of carbon dioxide. After filtration, the yellow filtrate was evaporated under reduced pressure.

The residual sticky brown oil was dissolved in glacial acetic acid (40 c.c.) and cautiously added to concentrated sulphuric acid (40 c.c.), excessive rise in temperature being avoided. This mixture was added dropwise during 30 min. at 5° to a stirred solution prepared by dissolution of sodium nitrite (13·2 g.) in concentrated sulphuric acid (40 c.c.; pre-cooled to 0°) and dilution with glacial acetic acid (80 c.c.). After a further hr. stirring the solution was added to a vigorously stirred mixture of sodium iodide (60 g.), iodine (50 g.), urea (40 g.), water (500 c.c.), and chloroform (250 c.c.); the temperature rose to *ca.* 35°. Stirring was continued for 1 hr., then the chloroform layer was collected and the aqueous residue extracted with more chloroform (3 × 100 c.c.). The extract was washed with water, covered with a solution of sodium metabisulphite, and sulphur dioxide was bubbled through it until the excess of iodine was removed. The solution was then washed with water, dried, and evaporated, to leave a yellow solid. Crystallisation from ethanol gave 3 : 5-di-iodoanisole (13·9 g., 48%) as tablets, m. p. 83—84° (Found : I, 70·3. Calc. for $C_7H_6OI_2$: I, 70·5%). (Hodgson and Wignall, *J.*, 1926, 2077, give m. p. 85°.)

3 : 5-*Di-iodophenol.*—3 : 5-Di-iodoanisole (10 g.) in 57% hydriodic acid (30 c.c.) and glacial acetic acid (45 c.c.) was refluxed for 2 hours. The solution was poured into water, and the solid extracted into chloroform. The oily solid left after removal of the solvent was crystallised from light petroleum (b. p. 80—100°), to give 3 : 5-di-iodophenol (7·2 g., 75%) as needles, m. p. 102—104° (Brenans, *Compt. rend.*, 1903, **136**, 236, gives m. p. 103—104°).

N-Acetyl-4-(3 : 5-*di-iodophenoxy*)-3 : 5-*dinitro*-DL-*phenylalanine Ethyl Ester* (XIII; X = I, R = Et).—The quaternary salt (I*a*) was prepared as described above from *N*-acetyl-3 : 5-dinitro-DL-tyrosine ethyl ester (3 g.). The gum was dissolved in dry chloroform (30 c.c.) and pyridine (12 c.c.), and 3 : 5-di-iodophenol (9 g.) was added. After 48 hr. refluxing, the product was isolated as described for compound (XIII; X = NO_2, R = Et). The *diphenyl ether* (4 g., 68%) separated from ethanol as needles, m. p. 201° (Found : C, 34·3; H, 2·7; N, 6·2. $C_{19}H_{17}O_8N_3I_2$ requires C, 34·1; H, 2·6; N, 6·3%).

From the alkaline washings most of the unused 3 : 5-di-iodophenol could be recovered by acidification.

4-(3 : 5-*Di-iodophenoxy*)-3 : 5-*dinitro*-DL-*phenylalanine.*—The above acetamido-ester (2 g.), glacial acetic acid (20 c.c.), and concentrated hydrochloric acid (20 c.c.) were refluxed for 2 hr. then diluted with a little water. The solid which had separated was collected and dried. Crystallisation from aqueous pyridine gave the *amino-acid* (1·7 g., 95%) as plates, m. p. 227° (decomp.) (Found : C, 30·0; H, 2·2; N, 6·6; I, 41·8. $C_{15}H_{11}O_7N_3I_2$ requires C, 30·2; H, 1·9; N, 7·0; I, 42·3%).

N-Acetyl-4-(3 : 5-*di-iodophenoxy*)-3 : 5-*dinitro*-DL-*phenylalanine* (XIII; X = I, R = H).—A solution of the foregoing amino-acid (0·5 g.) in N-sodium hydroxide (3·5 c.c.) was treated with acetic anhydride (0·25 c.c.), in portions, with vigorous shaking. A solid separated after a few min. and, after gentle warming (*ca.* 40°) to destroy excess anhydride, the mixture was acidified with hydrochloric acid, and the solid collected, washed with water, and dried. Crystallisation from glacial acetic acid gave the *acetamido-acid* as pale yellow needles, m. p. 245—246° (Found : C, 32·0; H, 2·1; N, 6·3; I, 39·0. $C_{17}H_{13}O_8N_3I_2$ requires C, 31·8; H, 2·0; N, 6·6; I, 39·6%).

N-Acetyl-4-(3 : 5-*di-iodophenoxy*)-3 : 5-*di-iodo*-DL-*phenylalanine Ethyl Ester* (XV; R = Et, R′ = Ac).—*N*-Acetyl-4-(3 : 5-di-iodophenoxy)-3 : 5-dinitro-DL-phenylalanine ethyl ester (5 g.) was dissolved in boiling glacial acetic acid (300 c.c.) and then stirred while the temperature dropped to 30°. All subsequent operations were carried out in an atmosphere of carbon dioxide. Iron powder (10 g.) was added in one portion, followed by concentrated hydrochloric acid (60 c.c.) in 5-c.c. portions during an hr., too great a rise in temperature being avoided. The mixture was stirred for a further hr., filtered to remove inorganic residues, and concentrated to small bulk (20 c.c.) under reduced pressure. An excess of saturated sodium hydrogen carbonate solution was added, then, after being shaken with chloroform (200 c.c.), the whole mixture was filtered to remove some dark insoluble material. The chloroform extract was dried and evaporated, leaving the diamine as a light brown glass, m. p. *ca.* 95°. The product was dissolved in a mixture of glacial acetic acid (25 c.c.) and concentrated sulphuric acid (25 c.c.) and added dropwise during 30 min. to a cooled, stirred solution of sodium nitrite (1·0 g.) in concentrated sulphuric acid (15 c.c.) diluted with acetic acid (15 c.c.). After being stirred for a further 2 hr. at 0°, the solution was added to sodium iodide (3 g.), iodine (3·5 g.), urea (5 g.), water (150 c.c.), and chloroform (200 c.c.) with vigorous stirring. The temperature rose to *ca.* 40° and after an hr. the chloroform layer was run off and the aqueous residue extracted with more chloroform. Excess of iodine was removed by treatment with sodium

metabisulphite solution. The combined chloroform layers gave, on evaporation, a yellow brown solid which was dissolved in boiling ethanol. The *tetra-iodo*-compound (2·44 g., 39%) separated as needles, m. p. 184—186° (Found: C, 27·7; H, 2·3; N, 1·7; I, 60·6. $C_{19}H_{17}O_4NI_4$ requires C, 27·5; H, 2·1; N, 1·7; I, 61·1%).

4-(3 : 5-*Di-iodophenoxy*)-3 : 5-*di-iodo*-DL-*phenylalanine* (XV; R = R′ = H).—A solution of the above acetamido-ester (1 g.) in a mixture of acetic acid (10 c.c.) and concentrated hydrochloric acid (10 c.c.) was boiled under reflux for 2 hr. A little water was added and the solid was filtered off and dried. It was purified by dissolving it in a boiling mixture of equal volumes of ethanol and 2N-sodium hydroxide and adding 2N-hydrochloric acid until the pH was 4—5. The *amino-acid* (0·61 g., 67%) melted at 223—225° (decomp.) (Found: C, 24·1; H, 1·9; N, 1·8; I, 65·6. $C_{15}H_{11}O_3NI_4$ requires C, 23·7; H, 1·5; N, 1·8; I, 66·7%).

Methyl 4′-*Methoxy*-2 : 6-*dinitrodiphenyl*-4-*carboxylate* (XVI).—A mixture of methyl 4-chloro-3 : 5-dinitrobenzoate (65 g.) and *p*-iodo-anisole (75 g.) was heated at 230—240° and copper-bronze (75 g.) was added in portions. The mixture was then kept at 235—240° for 30 min. After cooling, the solid was extracted with boiling acetone, and the extract was evaporated to dryness. The residual brown gum was dissolved in benzene and chromatographed on alumina. The solid residue obtained by evaporation of the benzene eluate was crystallised from alcohol, to give 40·9 g. (49%) of *methyl* 4′-*methoxy*-2 : 6-*dinitrodiphenyl*-4-*carboxylate*, m. p. 132—133°. Further crystallisation from alcohol gave yellow needles, m. p. 133—135° (Found: C, 54·3; H, 3·5; N, 8·4. $C_{15}H_{12}O_7N_2$ requires C, 54·2; H, 3·6; N, 8·4%).

The mother-liquors from the crystallisation of the crude diphenyl gave a small quantity of methyl 3 : 5-dinitrobenzoate, m. p. 110—112°, alone or mixed with an authentic specimen.

The diphenyl derivative (0·5 g.) was hydrolysed under reflux with concentrated hydrochloric acid (2·5 c.c.) and acetic acid (2·5 c.c.). The ester dissolved during about 1 hr. and after another 30 min. the solution was diluted with water to give an oil which rapidly solidified. Crystallisation from a mixture of ethyl acetate and light petroleum (b. p. 60—80°) gave 4′-*methoxy*-2 : 6-*dinitrodiphenyl*-4-*carboxylic acid*, m. p. 250—253° (Found: N, 8·8; OMe, 10·3. $C_{14}H_{10}O_7N_2$ requires N, 8·8; OMe, 9·75%).

Methyl 2 : 6-*Diamino*-4′-*methoxydiphenyl*-4-*carboxylate* (XVII; R = CO_2Me).—The above dinitro-compound (20·7 g.) in glacial acetic acid (400 c.c.) was hydrogenated (<1 hr. required) in the presence of palladised charcoal (10%; 2 g.). The solution was filtered, this and subsequent operations being conducted under carbon dioxide. The filtrate was evaporated to dryness under reduced pressure at about 50°. Crystallisation of the residual solid from benzene–light petroleum (b. p. 40—60°) gave the *diamine* (15·6 g., 92%) as brown crystals, m. p. 161—163°. Further crystallisation from the same solvents gave material melting constantly at 166·5—168° but still pale brown (Found: C, 66·2; H, 5·7; N, 10·35. $C_{15}H_{16}O_3N_2$ requires C, 66·1; H, 5·9; N, 10·3%).

The *diacetyl* derivative was prepared by treatment of the diamine (0·12 g.) with acetic anhydride (0·25 g.) in dry pyridine (2 c.c.) at room temperature for 16 hr. The crystals were filtered off, washed with 2N-hydrochloric acid and water, and dried. Crystallisation from a mixture of chloroform and a little light petroleum gave colourless needles, m. p. 253·5—254° (Found: N, 7·7; OMe, 17·0. $C_{19}H_{20}O_5N_2$ requires N, 7·9; OMe, 17·4%).

Methyl 2 : 6-*Di-iodo*-4′-*methoxydiphenyl*-4-*carboxylate* (XVIII; R = CO_2Me).—The foregoing diamine (14·9 g.) was warmed with glacial acetic acid (48 c.c.) and concentrated sulphuric acid (24 c.c.); a little material which remained undissolved was taken up in hot glacial acetic acid and was added to the acetic–sulphuric acid. The solution of the diamine was added, with stirring, at −2° to 0°, during about 90 min. to a solution of nitrosylsulphuric acid prepared from sodium nitrite (9·6 g.), concentrated sulphuric acid (72 c.c.), and acetic acid (144 c.c.). The orange-coloured solution was then stirred at 0° for 1 hr. and added during about 30 min. from an ice-cooled dropping funnel to a vigorously stirred solution of iodine (40 g.), sodium iodide (48 g.), urea (7 g.), and water (750 c.c.) covering a layer of chloroform (400 c.c.). The mixture was stirred overnight at room temperature, the chloroform layer was then separated, and the aqueous layer extracted twice with chloroform. The combined extracts were washed with a concentrated aqueous solution of sodium thiosulphate to remove iodine, then twice with water, and were dried ($CaCl_2$). The solution was evaporated to dryness and the brownish residue was chromatographed in benzene on alumina, with benzene as eluant. The coloured impurities remained near the top of the column while the required *di-iodo*-compound was rapidly eluted. Crystallisation from glacial acetic acid gave colourless prisms (19·9 g.), m. p. 174—176°, and a second crop which, after further crystallisation, yielded a further 0·8 g. of material, m. p. 172—175° (77% in all). Further crystallisation from glacial

acetic acid gave prisms, m. p. 175—176° (Found: C, 36·6; H, 2·3; I, 51·0. $C_{15}H_{12}O_3I_2$ requires C, 36·5; H, 2·45; I, 51·4%).

The corresponding *acid*, prepared by hydrolysis with aqueous-alcoholic sodium hydroxide, separated from aqueous alcohol as colourless needles, m. p. 223—225° (Found: C, 35·3; H, 2·4. $C_{14}H_{10}O_3I_2$ requires C, 35·0; H, 2·1%).

4′-Hydroxy-2 : 6-di-iododiphenyl-4-carboxylic Acid (XXII; X = H).—Methyl 2 : 5-di-iodo-4′-methoxydiphenyl-4-carboxylate (1·0 g.) was boiled under reflux for 2 hr. with constant-boiling hydriodic acid (5 c.c.) and acetic acid (5 c.c.). The ester went partly into solution at first but a light powdery solid soon began to separate. After cooling, the solid was filtered off, washed with water, and dried. After two crystallisations from 50% acetic acid it was obtained in almost theoretical yield as glistening plates, m. p. 268—271° (Found: C, 33·8; H, 2·1; I, 54·9. $C_{13}H_8O_3I_2$ requires C, 33·5; H, 1·7; I, 54·5%).

4′-Hydroxy-2 : 6 : 3′ : 5′-tetra-iododiphenyl-4-carboxylic Acid (XXII; X = I).—4′-Hydroxy-2 : 6-di-iododiphenyl-4-carboxylic acid (0·47 g.) in aqueous ethylamine (20%; 10 c.c.) was shaken while a solution of iodine (0·55 g.) in aqueous sodium iodide was added dropwise. A colourless solid began to separate towards the end of the addition. The mixture was kept for 10 min., the solid was brought into solution by warming, and the solution was acidified to Congo-red with hydrochloric acid. The solid (0·73 g.) crystallised from acetic acid as colourless needles, m. p. 264—265° (decomp.) (Found: C, 22·2; H, 1·1; I, 70·7. $C_{13}H_6O_3I_4$ requires C, 21·75; H, 0·8; I, 70·7%).

4-Acetoxymethyl-2 : 6-di-iodo-4′-methoxydiphenyl (XVIII; R = CH_2·OAc) (*by Reduction of Methyl 2 : 6-Di-iodo-4′-methoxydiphenyl-4-carboxylate*).—The ester (1·0 g., 0·002 mole) in dioxan (distilled over sodium; 15 c.c.) was added fairly rapidly with stirring to ice-cold ethereal lithium aluminium hydride (2·16%; 3·5 c.c.; 0·002 mole). The mixture was then stirred at 0° for 30 min. and decomposed with ice. 2N-Sulphuric acid was added and the solution extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and evaporated. The residual brown gum (0·88 g.) which did not crystallise, was chromatographed in benzene on a short column of alumina. Benzene eluted only a trace of gum, but 10% of methanol in benzene readily eluted 682 mg. of a gum. This was acetylated by acetic anhydride (1 c.c.) for 1 hr. on the water-bath. Excess of anhydride was destroyed by refluxing ethanol, and the solution was diluted with water and extracted with chloroform. The extract was washed with sodium hydrogen carbonate solution and with water, and was dried ($MgSO_4$). After removal of the solvent the residue was dissolved in boiling light petroleum (b. p. 60—80°), and the solution was decanted from a little gum which separated first. On further cooling, the *acetoxymethyl* compound separated in needles, m. p. 117—119° (Found: C, 38·0; H, 2·7; I, 49·3. $C_{16}H_{14}O_3I_2$ requires C, 37·8; H, 2·8; I, 50·0%).

An experiment, with 1·4 g. (0·00282 mole) of the ester and 0·00168 mole of lithium aluminium hydride gave 0·58 g. of unchanged ester, which was readily eluted by benzene, and, after acetylation, 0·29 g. of the acetoxymethyl compound.

Ethyl α-Acetamido-α-carbethoxy-β-(2 : 6-di-iodo-4′-methoxy-4-diphenylyl)propionate (XIX).—Methyl 2 : 6-di-iodo-4′-methoxydiphenyl-4-carboxylate (5 g.) in dry dioxan (75 c.c.) was reduced as described above, with lithium aluminium hydride in ether (2·2% solution; 13·5 c.c.). Chromatography of the crude product on alumina gave 1·71 g. of unchanged ester, with 2·28 g. of crude alcohol which was eluted with 5% methanol in ether. This crude alcohol in dry benzene (20 c.c.) was treated with thionyl chloride (1·2 c.c.), and the solution was boiled under reflux for 3 hr. The solution was evaporated to dryness under reduced pressure, and the last traces of thionyl chloride were removed by repeated evaporation with benzene.

Sodium (0·12 g.) was dissolved in dry ethanol (5 c.c.), and ethyl acetamidomalonate (1·08 g.) was added. The crude chloro-compound was not very soluble even in hot ethanol but it was added to the sodio-acetamidomalonic ester solution with the help of about 25 c.c. of boiling ethanol. The mixture was boiled under reflux and stirred for 6 hr. A small quantity of solid separated during this time. The hot solution was filtered and evaporated to small bulk. On cooling, a powdery solid separated which was filtered off and washed with ethanol. After crystallisation from aqueous acetic acid the *malonic ester* (0·50 g., 11% based on unrecovered starting material) melted at 205—209° (Found: N, 2·2; I, 37·6. $C_{23}H_{25}O_6NI_2$ requires N, 2·1; I, 38·2%).

4-p-Hydroxyphenyl-3 : 5-di-iodo-DL-phenylalanine (XX).—Ethyl α-acetamido-α-carbethoxy-β-(2 : 6-di-iodo-4′-methoxy-4-diphenylyl)propionate (0·34 g.) was boiled under reflux for 3 hr. with constant-boiling hydriodic acid (2 c.c.) and acetic acid (2 c.c.). The solution was evaporated to dryness, the residual solid dissolved in alcohol, and the solution diluted with

water and brought to pH 5 by addition of sodium acetate solution. On cooling, a powdery solid (0·19 g., 67%) separated, which was filtered off and washed well with water. It decomposed at 196—199° (Found: C, 37·1; H, 3·3; N, 2·6; I, 45·9. $C_{15}H_{13}O_3NI_2,C_2H_6O$ requires C, 36·8; H, 3·4; N, 2·5; I, 45·7%).

4-(4-*Hydroxy*-3 : 5-*di-iodophenyl*)-3 : 5-*di-iodo*-DL-*phenylalanine* (XXI).—4-*p*-Hydroxyphenyl-3 : 5-di-iodophenylalanine (93·5 mg.) in aqueous ethylamine (33%; 1 c.c.) was treated with a solution of iodine in aqueous potassium iodide (1·26N; 0·60 c.c.), gradually with shaking. The iodine was decolorised and towards the end of the addition a white solid started to separate. The mixture was left overnight in the refrigerator, and the solid was then filtered off and suspended in water. Hydrochloric acid (0·2N) was added till the pH was 5 and after some hours the solid was filtered off, washed with water, and dried in a desiccator. It was purified by dissolving it in hot N-sodium hydroxide (1 c.c.), filtering, and adding N-hydrochloric acid to the boiling alkaline solution to bring the pH to 5. After some time in the refrigerator, the nearly colourless solid was filtered off, washed thoroughly with water, and dried at 80°/0·1 mm. The *amino-acid* melted at 202—203° (decomp.) (Found: C, 22·9; H, 1·9; I, 65·2. $C_{15}H_{11}O_3NI_4,H_2O$ requires C, 23·1; H, 1·7; I, 65·2%).

2 : 6-*Diamino*-4-*hydroxymethyl*-4′-*methoxydiphenyl* (XVII; R = CH_2·OH).—A solution of methyl 2 : 6-diamino-4′-methoxydiphenyl-4-carboxylate (6·8 g.) in dry dioxan (250 c.c.) was added to a stirred solution of lithium aluminium hydride in ether (2·28%; 125 c.c.), under nitrogen. The mixture was boiled under reflux for 1 hr., cooled, and decomposed with ice followed by 40% sodium hydroxide solution. The mixture was extracted with chloroform, and the extract washed with water, dried, and evaporated to a brownish gum which crystallised from chloroform–light petroleum (b. p. 60—80°). The *diamine* (4·7 g., 77%) melted at 150—151° after further crystallisation (Found: C, 68·5; H, 6·7; N, 11·45. $C_{14}H_{16}O_2N_2$ requires C, 68·8; H, 6·6; N, 11·5%).

4-*Acetoxymethyl*-2 : 6-*di-iodo*-4′-*methoxydiphenyl* (XVIII; R = CH_2·OAc) (With Dr. J. Attenburrow).—The above diamine (3·4 g.) was tetrazotised in acetic acid (17 c.c.) with sodium nitrite (2·5 g.) in concentrated sulphuric acid (23·5 c.c.) and acetic acid (30 c.c.). The resulting tetrazonium solution was added fairly rapidly to a solution of iodine (9·6 g.), sodium iodide (11·4 g.) and urea (1·42 g.) in water (186 c.c.) covering a layer of chloroform (45 c.c.). The mixture was then stirred for 90 min. and sodium metabisulphite was added, to destroy excess of iodine. The aqueous layer was extracted with chloroform; the combined chloroform solutions were washed with sodium metabisulphite solution and water (formation of emulsions caused some difficulty). The dried solution was evaporated to a brown gum which was chromatographed in benzene on alumina. Elution with benzene gave 4-acetoxymethyl-2 : 6-di-iodo-4′-methoxydiphenyl (2·64 g.) melting at 115—119°. A further quantity (0·86 g.) was obtained by elution with acetone and treatment of the eluate with excess of acetic anhydride on the steam-bath for 1 hr., followed by chromatography of the crude material on alumina. The total yield was 3·5 g., 49%. The m. p. was unchanged after crystallisation of the compound from alcohol (Found: I, 49·6. Calc. for $C_{16}H_{14}O_3I_2$: I, 50·0%).

4-*Hydroxymethyl*-2 : 6-*di-iodo*-4′-*methoxydiphenyl* (XVIII; R = CH_2·OH).—The acetate (7·6 g.) was boiled under reflux for 3 hr. with potassium hydroxide (7·6 g.) in 90% ethanol (76 c.c.). The solution was diluted with water and extracted with ether. The extract was washed with dilute sulphuric acid and evaporated. Crystallisation of the residue from benzene–light petroleum (b. p. 40—60°) gave the *alcohol* (6·1 g., 87%), which melted at 101° after further crystallisation (Found: C, 36·3; H, 2·75; I, 54·0. $C_{14}H_{12}O_2I_2$ requires C, 36·1; H, 2·6; I, 54·5%).

Potassium 4-*Hydroxy*-3 : 5-*dimethylphenyl Sulphate* (XXIII).—Ammonium persulphate (190 g.) in water (2 l.) was added dropwise during 4 hr. to a solution of 2 : 6-dimethylphenol (100 g.) in 4N-potassium hydroxide (1 l.) kept below 20°. Having been stirred overnight the solution was brought to pH 5 with acetic acid, extracted with ether, made alkaline again with potassium hydroxide, and evaporated to dryness at the water pump, and the dark residue was dissolved in boiling alcohol (400 c.c.). On cooling, the solution deposited crystals of the required *potassium* salt. Two further crops were got by concentration of the mother-liquors, giving a total of 156 g. (74%) of crude product. Recrystallisation from alcohol containing a trace of water gave colourless crystals (Found: C, 36·1; H, 3·6; K, 14·6. $C_8H_9O_5SK$ requires C, 37·5; H, 3·5; K, 15·2%).

2 : 6-*Dimethylquinol* (XXIV; R = H).—The crude potassium sulphate (50 g.), dissolved in 2N-hydrochloric acid (250 c.c.), was heated on the steam-bath for 90 min. The cooled solution was twice extracted with ether, and the extract was evaporated. Recrystallisation of

the residue from water (charcoal) gave the quinol (8·0 g., 30%, *i.e.*, 22% overall from the phenol), m. p. 151—152° (Stern *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 869, give m. p. 147—149°).

*N-Acetyl-3′ : 5′-dimethyl-3 : 5-dinitro-*DL*-thyronine Ethyl Ester* (XXV; R = H).—*N*-Acetyl-3 : 5-dinitro-DL-tyrosine ethyl ester (4·2 g.) was heated with toluene-*p*-sulphonyl chloride (2·6 g.) in pyridine (25 c.c.) at 100° for 1 hr. 2 : 6-Dimethylquinol (6·0 g.) was then added, and the mixture was boiled gently for 2 hr. When the mixture was poured into dilute hydrochloric acid a dark gum was precipitated. It was washed with water and extracted with ethyl acetate. After evaporation of the solvent the residue was extracted with a mixture of benzene (100 c.c.) and ethyl acetate (50 c.c.) and the extract was passed down a column of activated alumina. The column was developed with benzene–ethyl acetate (2 : 1) and then ethyl acetate alone. The gums obtained by evaporation of two of the middle fractions showed signs of crystallising. They were therefore dissolved in benzene and chromatographed again. The middle fractions from the second chromatogram partly crystallised. After two crystallisations from ethyl acetate–*cyclo*hexane the *ester* formed golden-yellow blades, m. p. 161° (Found : C, 55·0; H, 5·3; N, 9·1. $C_{21}H_{23}O_9N_3$ requires C, 54·7; H, 5·0; N, 9·1%).

In a second experiment the product was obtained solid at once, but melted over a very wide range and could not be purified by repeated recrystallisation.

4-Benzyloxy-3 : 5-dimethylphenol (XXIV; R = CH_2Ph).—Benzyl chloride (7 c.c.) was dropped during 2½ hr. into a stirred, boiling solution of potassium 4-hydroxy-3 : 5-dimethylphenyl sulphate (10 g.) and sodium hydroxide (2·8 g.) in water (20 c.c.) and alcohol (25 c.c.). After another 90 min. the solution was made just acid to Congo-red with hydrochloric acid and boiled for 2 hr. more, whereupon a black oil separated from which steam-distillation removed only benzyl alcohol. The aqueous layer was decanted from the tar, which was extracted with ether. The residue from evaporation of the ether was crystallised twice from carbon tetrachloride, to yield the colourless *benzyl ether* (1·6 g., 18%), m. p. 87—88° (Found : C, 78·2; H, 6·9. $C_{15}H_{16}O_2$ requires C, 78·9; H, 7·1%).

*N-Acetyl-4-(4-benzyloxy-3 : 5-dimethylphenoxy)-3 : 5-dinitro-*DL*-phenylalanine Ethyl Ester* (XXV; R = CH_2Ph).—4-Benzyloxy-2 : 6-dimethylphenol (1·35 g., 2 mols.) was added to a solution of *N*-acetyl-3 : 5-dinitro-DL-tyrosine ethyl ester (1·0 g.) and toluene-*p*-sulphonyl chloride (0·62 g., 1·1 mol.) in dry pyridine (25 c.c.) which had been heated on the steam-bath for 30 min. After 90 min.' refluxing the mixture was cooled, diluted with chloroform (100 c.c.), and extracted with dilute hydrochloric acid and sodium carbonate solution. The chloroform was removed under reduced pressure and the residual gum chromatographed in acetone on activated alumina. The yellow fraction which was not adsorbed was evaporated to dryness and the yellow gum crystallised twice from chloroform–*cyclo*hexane. The *diphenyl ether* (1·1 g., 68%) formed pale yellow crystals, m. p. 118—121° (Found : C, 61·2; H, 5·3; N, 7·7. $C_{28}H_{29}O_9N_3$ requires C, 61·0; H, 5·3; N, 7·6%).

*3′ : 5′-Dimethyl-3 : 5-dinitro-*DL*-thyronine* (XXVIII).—(*a*) A solution of the above ester (0·5 g.) in ethanol (10 c.c.) and hydrochloric acid (5 c.c.) was heated under reflux for 3½ hr., then concentrated to dryness under reduced pressure, and the residue was dissolved in a little ethanol, the pH being adjusted to 5 by the addition of sodium acetate solution. Addition of water precipitated a yellow solid which, on crystallisation from ethanol, yielded the yellow *amino-acid*, m. p. 203—207° (decomp.) (Found : C, 52·5; H, 4·7; N, 10·1. $C_{17}H_{17}O_8N_3,\frac{1}{2}C_2H_6O$ requires C, 52·2; H, 4·9; N, 10·1%). Dilution of the alcoholic mother-liquor with water yielded a small quantity of yellow solid, m. p. 163°, probably the *O*-benzyl compound.

(*b*) A mixture of *N*-acetyl-3′ : 5′-dimethyl-3 : 5-dinitro-DL-thyronine ethyl ester (0·2 g.), ethanol (2 c.c.), concentrated hydrochloric acid (1 c.c.), and water (1 c.c.) was boiled under reflux for 2 hr. Most of the ethanol was removed by distillation and the residue was allowed to cool, whereupon an oil separated which later solidified. It recrystallised from dilute hydrochloric acid as a mixture of yellowish prisms and fine colourless needles, the latter in very small amount. It was possible to remove the needles by decantation. The residual crystals were covered with water, and 2N-sodium hydroxide was added with shaking until the solid had completely dissolved. On addition of hydrochloric acid to the dark solution, fine yellow needles started to be precipitated as soon as the colour had disappeared. Excess of hydrochloric acid was added and the solid was filtered off and recrystallised from water. The orange-yellow crystals darkened on heating at about 200° and melted with decomposition at 216°.

A mixture of the compounds prepared by methods (*a*) and (*b*) melted between the m. p.s of the constituents.

4-Methoxy-3 : 5-dimethylphenol (XXIV; R = Me).—A mixture of potassium 4-hydroxy-

3 : 5-dimethylphenyl sulphate (20 g.), 90% alcohol (320 c.c.) and methyl sulphate (80 c.c.) was stirred and cooled while 40% sodium hydroxide (250 c.c.) was added during 1 hr. Next morning the mixture was heated on the steam-bath for 30 min., cooled, acidified with concentrated hydrochloric acid, and re-heated for 30 min. Steam-distillation produced a milky distillate which was extracted with ether. Evaporation of the ether left the methoxy-compound (4·5 g., 38%), which melted at 83° after recrystallisation from water (Baker and Brown, *J.*, 1948, 2303, give m. p. 83°).

*N-Acetyl-4-(4-methoxy-3 : 5-dimethylphenoxy)-3 : 5-dinitro-*DL*-phenylalanine Ethyl Ester* (XXV; R = Me).—4-Methoxy-3 : 5-dimethylphenol (1·2 g.) was added to a solution of *N*-acetyl-3 : 5-dinitro-DL-tyrosine ethyl ester (1·0 g.) and toluene-*p*-sulphonyl chloride (0·62 g.) in pyridine (25 c.c.) which had been heated on the steam-bath for 30 min. When it had been boiled for 2 hr. the mixture was poured into dilute hydrochloric acid and extracted with chloroform. The gum remaining from evaporation of the chloroform was dissolved in acetone and passed down a column of alumina. The pale yellow solution which passed straight through was evaporated and the residue was recrystallised twice from aqueous alcohol. The *diphenyl ether* (0·89 g., 53%) was obtained as yellow crystals, m. p. 116—120° (Found: C, 55·9; H, 5·4; N, 8·5. $C_{22}H_{25}O_9N_3$ requires C, 55·6; H, 5·3; N, 8·8%).

*N-Acetyl-3 : 5-di-iodo-4-(4-methoxy-3 : 5-dimethylphenoxy)-*DL*-phenylalanine Ethyl Ester* (XXVI; R = Me).—The dinitro-compound (1·0 g.) in acetic acid (50 c.c.) was hydrogenated in the presence of palladised charcoal (0·5 g.) at room temperature and pressure. After 40 hr. the uptake of hydrogen was almost theoretical. Sulphuric acid (20 c.c.) was gradually added to the solution with cooling, and the resulting mixture was added during 45 min. to a solution of sodium nitrite (0·35 g.; 2·4 mols.) in sulphuric acid (50 c.c.) and acetic acid (50 c.c.) kept at −5°. After 90 min. this tetrazonium solution was run into a stirred mixture of water (300 c.c.) and chloroform (150 c.c.) containing iodine (5 g.) and sodium iodide (5 g.). Half an hour later the chloroform was separated, washed with sodium metabisulphite, and then water, and evaporated to dryness. The residue, in acetone, was passed down a column of activated alumina. Evaporation of the solvent left a yellow gum, that solidified when scratched under light petroleum. The *di-iodo*-compound (0·62 g., 46%) formed pale buff crystals, melting at 149—151° after recrystallisation from aqueous alcohol (Found: C, 41·4; H, 4·2; I, 39·1. $C_{22}H_{25}O_5NI_2$ requires C, 41·4; H, 3·9; I, 39·9%).

3 : 5-*Di-iodo-3′ : 5′-dimethyl-*DL*-thyronine* (XXVII).—A solution of the acetamido-ester (1·8 g.) in acetic acid (12 c.c.) and constant-boiling hydriodic acid (8 c.c.) was boiled for 3½ hr. The residue left after removal of the solvents under reduced pressure was dissolved in boiling alcohol containing a trace of sodium metabisulphite, and sodium acetate solution was added until the pH reached 5. The gelatinous precipitate was filtered off and washed thoroughly with water. It was redissolved in alcoholic hydrochloric acid and brought out of solution again with sodium acetate, to give the colourless *amino-acid* (1·2 g., 75%), m. p. 230—233° (decomp.) (Found: C, 35·9; H, 3·5; I, 44·6. $C_{17}H_{17}O_4NI_2.H_2O$ requires C, 35·7; H, 3·3; I, 44·45%).

After only 2 hr. boiling a compound melting at about 160° could be isolated from the mother-liquors after removal of the above amino-acid. Since it gave the amino-acid on further boiling with hydriodic and acetic acids, it must have been the *O*-methyl-amino-acid.

*N-Acetyl-3 : 5-dicyano-4-*p*-methoxyphenoxy-*L*-phenylalanine Ethyl Ester* (XXIX; R = CN).—A solution of *N*-acetyl-3 : 5-di-iodo-4-*p*-methoxyphenoxy-L-phenylalanine ethyl ester (50 g.) in pyridine (75 c.c.) containing cuprous cyanide (25 g.) was refluxed for 6 hr. The semi-solid mass was poured into water, and the solid was filtered off and washed with water. It was then added to 2N-ammonia (500 c.c.) and chloroform (300 c.c.), and the mixture was stirred thoroughly. After filtration of the mixture through kieselguhr, the chloroform layer was separated, washed successively with 2N-ammonia, 2N-hydrochloric acid, and water, and was dried (K_2CO_3). The solvent was removed and the residue crystallised from ethanol (charcoal). The *dicyano*-compound (27 g., 81%) had m. p. 139—140° and $[\alpha]_D$ +58° (*c*, 1·24 in $CHCl_3$) (Found: C, 64·6; H, 5·4; N, 10·1. $C_{22}H_{21}O_5N_3$ requires C, 64·9; H, 5·2; N, 10·3%).

3 : 5-*Dicarboxy-*L*-thyronine.*—A solution of *N*-acetyl-3 : 5-dicyano-4-*p*-methoxyphenoxy-L-phenylalanine ethyl ester (5 g.) in boiling hydriodic acid (*d* 1·7; 50 c.c.) was refluxed for 6 hr. The solvent was then distilled off and the residue was dissolved in 2N-sodium carbonate. Addition of 2N-hydrochloric acid precipitated a solid which was filtered off, washed, and purified by reprecipitation. The *acid* did not melt at 360° and was not soluble in any of the usual solvents. It had $[\alpha]_D^{24}$ +19° (*c*, 1·06 in 2N-Na_2CO_3) (Found: C, 56·3; H, 4·0; N, 3·7. $C_{17}H_{15}O_8N$ requires C, 56·5; H, 4·2; N, 3·9%).

3-Iodo-2-p-methoxyphenoxy-5-methylbenzoic acid (XXX; R = CO_2H).—Magnesium (0·36 g.) was added to a solution of 2 : 6-di-iodo-4′-methoxy-4-methyldiphenyl ether (Part VIII, *J.*, 1951, 2467) (3·3 g.) in dry ether (40 c.c.). Attempts to start the reaction were unsuccessful, so a further quantity of magnesium (0·24 g.) was added and then methyl iodide (1·42 g.) in ether (14 c.c.) was run slowly on to the mixture. The mixture was gently refluxed for 24 hr., most of the magnesium dissolving. The product was poured on an excess of solid carbon dioxide, and the mixture set aside, then decomposed with ice and dilute hydrochloric acid, and extracted with ether. Extraction of the ethereal solution with sodium hydrogen carbonate solution, followed by acidification, gave the crude *acid* (1·2 g., 44%) which, after crystallisation from aqueous acetic acid and from *cyclo*hexane, was obtained as colourless needles, m. p. 184—185° (Found : C, 47·5; H, 3·75; I, 32·9. $C_{15}H_{13}O_4I$ requires C, 46·9; H, 3·4; I, 33·0%).

4′-Methoxy-2 : 6-dimethyldiphenyl ether (XXXI) (With MR. F. F. STEPHENS).—*p*-Iodoanisole (11·7 g.), 2 : 6-dimethylphenol (6·1 g.), copper bronze powder (0·1 g.), and anhydrous potassium carbonate (6·9 g.) were refluxed for 7 hr. The internal temperature was initially 216° and rose during the reaction to 242°. After cooling, the solid product was diluted with water and extracted with ether, and the extract washed with 2N-sodium hydroxide and water and evaporated. The residual dark brown oil was dissolved in ether and the solution passed down a column of alumina, which removed some dark brown material. The residue after evaporation of the ether was distilled and the fraction boiling between 155° and 193° at 14—16 mm. was collected. This fraction (6 g.) crystallised overnight and melted at 41—42° (after removal of a little oil on a porous tile). An analytical sample was obtained by fractional steam-distillation, followed by low-temperature crystallisation of the less volatile fraction from ether. The *diphenyl ether* was finally obtained as a colourless solid, m. p. 41·5—42·5° (Found : C, 78·8; H, 6·95. $C_{15}H_{16}O_2$ requires C, 78·9; H, 7·1%).

N-Acetyl-L-tyrosine Ethyl Ester.—A mixture of *N*-acetyl-L-tyrosine (du Vigneaud and Meyer, *J. Biol. Chem.*, 1932, **98**, 295) (20 g.), toluene-*p*-sulphonic acid (2 g.), ethanol (20 c.c.), and chloroform (500 c.c.) was boiled under reflux for 8 hr., the water formed in the reaction being removed azeotropically. The tyrosine derivative gradually dissolved. The resultant solution was washed with aqueous sodium hydrogen carbonate and water and was evaporated to dryness under reduced pressure. The residue was crystallised from aqueous methanol, giving colourless crystals of the ester monohydrate (21·5 g.; 89%), m. p. 84—87°, $[\alpha]_D^{20}$ +24° (*c*, 1 in EtOH) (Found, in material dried *in vacuo* at room temperature : C, 57·7; H, 7·0; N, 5·1. Calc. for $C_{13}H_{17}O_4N,H_2O$: C, 58·0; H, 7·1; N, 5·2%). A portion of the material was dried at 100° *in vacuo* (Found : C, 61·7; H, 6·7; N, 5·5. Calc. for $C_{13}H_{17}O_4N$: C, 62·1; H, 6·8; N, 5·6%). Thomas, MacAllister, and Niemann (*J. Amer. Chem. Soc.*, 1951, **73**, 1548) give m. p. 96—97°, $[\alpha]_D^{25}$ +24·7°; Kaufman, Neurath, and Schwert (*J. Biol. Chem.*, 1949, **177**, 793) give m. p. 79—80°. The degree of hydration is not specified in either publication.

N-Acetyl-4-(4-methoxy-2 : 6-dinitrophenoxy)-L-phenylalanine Ethyl Ester (XXXIII).—A solution of 1-(2 : 6-dinitro-4-methoxyphenyl)pyridinium toluene-*p*-sulphonate (Part VII, *J.*, 1950, 2824) (24·5 g., 1 mol.) and *N*-acetyl-L-tyrosine ethyl ester monohydrate (27·5 g., 2 mol.) in pyridine (250 c.c.) was boiled under reflux for 90 min., then cooled and poured into dilute hydrochloric acid containing ice. The resulting gum was taken up in chloroform and the solution washed successively with 2N-hydrochloric acid, 2N-sodium hydroxide, and water. The solution was concentrated and passed through a short column of alumina; the product passed through rapidly and was obtained crystalline by evaporation. The *diphenyl ether* (14·8 g., 60%), obtained as yellow needles by recrystallisation from aqueous ethanol, had m. p. 134—135°, $[\alpha]_D^{20}$ +64·1 (*c*, 2·2 in $CHCl_3$) (Found : C, 53·95; H, 4·7; N, 9·2. $C_{20}H_{21}O_9N_3$ requires C, 53·7; H, 4·7; N, 9·4%). This material, after 2 weeks' storage, had m. p. 160—161°, and a later batch consisted of the higher-melting form.

When one molar proportion of the tyrosine derivative was employed, the yield was 37%.

N-Acetyl-4-(2 : 6-diamino-4-methoxyphenoxy)-L-phenylalanine Ethyl Ester.—The foregoing dinitro-compound (14·7 g.) in ethanol (750 c.c.) was hydrogenated at 90°/142 atm. for 3 hr., in the presence of palladised charcoal (3 g.). The suspension was filtered in an atmosphere of carbon dioxide and evaporated at <40° under reduced pressure, to an almost colourless syrup (12·0 g., 94%).

The *diacetyl* derivative, prepared by dissolving the diamine in boiling acetic anhydride and leaving the solution overnight at room temperature, separated from ethanol as colourless needles, m. p. 193°, $[\alpha]_D^{20}$ +53·8° (*c*, 2 in $CHCl_3$) (Found : C, 61·25; H, 6·5; N, 8·9. $C_{24}H_{29}O_7N_3$ requires C, 61·1; H, 6·2; N, 8·9%).

N-Acetyl-4-(2 : 6-di-iodo-4-methoxyphenoxy)-L-phenylalanine Ethyl Ester (XXXIV).—The

above diamine (8·0 g.) was dissolved in glacial acetic acid (80 c.c.) and concentrated sulphuric acid (15 c.c.), and the solution was added dropwise at 0° during 45 min. to a stirred solution of nitrosylsulphuric acid prepared from sodium nitrite (3·25 g.), sulphuric acid (30 c.c.), and acetic acid (25 c.c.) in the usual way. After a further hr. stirring the tetrazonium solution was added to a well-stirred mixture of sodium iodide (18·9 g.), iodine (16·8 g.), urea (3 g.), water (300 c.c.), and chloroform (300 c.c.). After being stirred for 2 hours the mixture was filtered from free iodine, and the chloroform layer was separated and washed successively with sodium metabisulphite solution, sodium hydrogen carbonate solution, and water. The chloroform solution was evaporated and the residue was passed, in chloroform, through a short alumina column. The desired product passed through rapidly and was recovered by evaporation. Crystallisation of this material from ethanol (charcoal) afforded the *di-iodo*-compound (6·8 g., 52%) as colourless needles, m. p. 171·5—172·5°, $[\alpha]_D^{19}$ +48·0° (*c*, 2 in $CHCl_3$) (Found: C, 39·3; H, 3·6; N, 2·3; I, 41·4. $C_{20}H_{21}O_5NI_2$ requires C, 39·4; H, 3·5; N, 2·3; I, 41·7%).

2′ : 6′-*Di-iodo*-L-*thyronine* (XXXV).—The above product (2 g.) in hydriodic acid (57%; 5 c.c.) and glacial acetic acid (5 c.c.) was boiled under reflux for 4 hr., and the solution evaporated to dryness under reduced pressure. The residue was taken up in hot water containing a little hydrochloric acid, and sodium metabisulphite was added to remove free iodine. Hot sodium acetate solution was then added until the pH was 4—5; a finely divided solid was precipitated. This was dissolved in hot 80% ethanol containing a little sodium hydroxide, and precipitated by adjustment of the pH to 4—5 by hot 0·5N-hydrochloric acid. The *amino-acid* (1·6 g., 93%), a nearly colourless powder, had m. p. 245—246° (decomp.) and $[\alpha]_D^{21}$ +6·5° [*c*, 1·9 in 1 : 1 (v/v) of N-HCl–EtOH] (Found: C, 34·5; H, 2·9; N, 2·7; I, 48·1. $C_{15}H_{13}O_4NI_2$ requires C, 34·3; H, 2·5; N, 2·7; I, 48·3%).

N-*Acetyl*-4-(2 : 6-*di-iodo*-4-*methoxyphenoxy*)-DL-*phenylalanine Ethyl Ester* (XXXIV).—Sodium (0·126 g.) was dissolved in dry ethanol (100 c.c.), *N*-acetyl-4-(2 : 6-di-iodo-4-methoxyphenoxy)-L-phenylalanine ethyl ester (3·05 g.) was added, and the solution was boiled under reflux for 3 hr. Chloroform (300 c.c.) was then added and the mixture, stirred and cooled in ice, was treated with 0·5N-hydrochloric acid, during a few min., until a faintly acid reaction was observed. Water was added and the chloroform layer was quickly separated and shaken briefly with N-sodium carbonate solution, and then with water. The chloroform layer, on evaporation under reduced pressure, afforded the desired *ester* (1·6 g., 52%) which was obtained as needles, m. p. 149—151°, by repeated recrystallisation from ethanol (Found: C, 39·3; H, 3·6; I, 42·15. $C_{20}H_{21}O_5NI_2$ requires C, 39·4; H, 3·5; I, 41·7%). The material was optically inactive.

2′ : 6′-*Di-iodo*-DL-*thyronine* (XXXV)—This material was obtained by hydrolysis of the foregoing DL-acetamido-ester by the method employed for the L-form. After repeated reprecipitation a nearly colourless powder was obtained, having m. p. 235° (decomp.). This material was optically inactive (Found: C, 34·35; H, 2·95; N, 2·5; I, 47·2. Calc. for $C_{15}H_{13}O_4NI_2$: C, 34·3; H, 2·5; N, 2·7; I, 48·3%). Niemann and McCasland (*J. Amer. Chem. Soc.*, 1944, **66**, 1870) give m. p. 220—221°.

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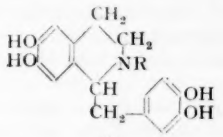
GLAXO LABORATORIES, LTD., GREENFORD, MIDDLESEX. [*Received, January* 14*th*, 1953.]

298. iso*Quinoline Alkaloids. Part I. The Oxidation of Tetrahydropapaveroline.*

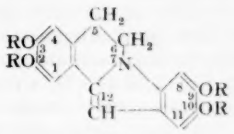
By John Harley-Mason.

Ferricyanide oxidation of tetrahydropapaveroline gives 5 : 6-dihydro-2 : 3 : 9 : 10-tetrahydroxydibenzo[*b*, *g*]pyrrocoline (II; R = H) which is readily further oxidised to the corresponding fully aromatic dibenzopyrrocoline (III; R = H).

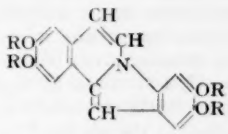
By oxidation of laudanosoline (I; R = Me) with chloranil Robinson and Sugasawa (*J.*, 1932, 789) obtained tetrahydro-2 : 3 : 9 : 10-tetrahydroxy-7-methyldibenzopyrrocolinium chloride (dehydrolaudanosoline), two hydrogen atoms being lost; two alkaloids derived from this structure have recently been described (Ewing, Hughes, Ritchie, and Taylor, *Nature*, 1952, **169**, 618). It was of interest in another connection to examine the oxidation of the corresponding unmethylated compound, tetrahydropapaveroline (I; R = H).



(I)

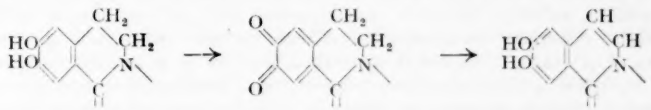


(II)



(III)

This was found to be oxidised very readily and conveniently by potassium ferricyanide with the loss of four hydrogen atoms giving 2 : 3 : 9 : 10-tetrahydroxy-5 : 6-dihydrodibenzo[*b*, *g*]pyrrocoline (II; R = H). The structure of this compound is shown by the identity of its almost colourless tetra-acetate (II; R = Ac) with the product obtained by Robinson and Sugasawa (*loc. cit.*) by the action of hot acetic anhydride on dehydrolaudanosoline, when demethylation and oxidation occur in addition to acetylation. It was found that (II; R = H) is very readily further oxidised; on exposure to air the material, originally pale yellow, very rapidly darkens, eventually becoming deep violet, and the same change occurs in ethyl acetate solution. Acetylation of the autoxidised material gave, after purification, a yellow tetra-acetate which contained less hydrogen than (II; R = Ac) and differed from it further in melting point and in exhibiting a strong bluish-green fluorescence in solution, whereas (II; R = Ac) fluoresces weakly violet. It was therefore formulated as 2 : 3 : 9 : 10-tetra-acetoxydibenzo[*b*, *g*]pyrrocoline (III; R = Ac). This was confirmed by the fact that the same product was obtained, though in very small yield, by ferricyanide oxidation of papaveroline and acetylation of the product.



This very ready aromatisation is of interest since in general 3 : 4-dihydro*iso*quinolines are not easily dehydrogenated (Openshaw and Wood, *J.*, 1952, **391**; Leonard and Leubner, *J. Amer. Chem. Soc.*, 1949, **71**, 3408). Further, it is noteworthy that only the tetraphenol (II; R = H) and not its tetra-acetate (II; R = Ac) is readily oxidised, suggesting that the hydroxyl groups participate in the oxidation. The mechanism indicated in the scheme is suggested, this being closely analogous to the aromatisation in the formation of dihydroxyindoles from 3 : 4-dihydroxyphenylethylamines of which the formation of (II; R = H) is, of course, itself an example. The formation of intensely coloured by-products during oxidation of (II; R = H) is undoubtedly due to the fact that the latter contains a 5 : 6-dihydroxyindole system which is readily oxidised to melanin-like products.

EXPERIMENTAL

Tetrahydropapaveroline Hydrobromide.—Tetrahydropapaverine hydriodide (Taylor, *J.*, 1952, 142) (5 g.) was refluxed for 2 hr. with hydrobromic acid (*d* 1·49; 35 c.c.). After cooling, the tetrahydropapaveroline hydrobromide, which formed colourless prisms, was collected. The product was free from iodide ion.

Oxidation of Tetrahydropapaveroline.—To a solution of the hydrobromide (1·8 g.) in water (200 c.c.), potassium ferricyanide (6 g.) and sodium hydrogen carbonate (1·6 g.) in water (200 c.c.) were added with stirring. A deep reddish-brown precipitate (probably tetrahydropapaveroline ferricyanide) was rapidly formed. The resulting suspension was quickly heated to 90° with continued stirring, most of the precipitate dissolving. The mixture was filtered hot, leaving a small amount of black residue, and a little sodium dithionite was added to the filtrate to prevent oxidation. After being kept overnight at 0°, the product which had separated as a yellow powder (0·9 g.) was recrystallised from ethyl acetate–light petroleum. 5 : 6-*Dihydro*-2 : 3 : 9 : 10-*tetrahydroxydibenzo*[b, g]*pyrrocoline* formed pale yellow prisms, m. p. 253—255° (decomp.) with preliminary darkening, soluble in ethanol and moderately soluble in ethyl acetate (Found: C, 66·6; H, 4·55; N, 5·0. $C_{16}H_{13}O_4N$ requires C, 67·0; H, 4·6; N, 4·95%). The solutions showed a violet fluorescence but soon became violet owing to oxidation. With Ehrlich's reagent an intense blue colour was given.

Acetylation (acetic anhydride–pyridine in the cold) gave the tetra-acetate which formed almost colourless prisms, m. p. 214—215° (from ethyl acetate), identical (mixed m. p.) with the material obtained from laudanosoline by Robinson and Sugasawa's (*loc. cit.*) method (Found: C, 64·0; H, 4·9. Calc. for $C_{24}H_{21}O_8N$: C, 63·85; H, 4·7%).

Further Oxidation.—A thin layer of the tetrahydroxy-compound (0·5 g.) was exposed on a watch-glass to the air for 2 days. The deep violet product thus obtained was acetylated, as above. Three recrystallisations from acetic acid–ethanol (charcoal) gave 2 : 3 : 9 : 10-*tetra-acetoxydibenzo*[b, g]*pyrrocoline* (0·25 g.), yellow prisms, m. p. 269—270° (Found: C, 63·75; H, 4·3; N, 3·0. $C_{24}H_{19}O_8N$ requires C, 64·1; H, 4·25; N, 3·1%), readily soluble in acetic acid and sparingly soluble in ethanol; the solutions showed a strong bluish-green fluorescence. With Ehrlich's reagent a weak greenish colour was given.

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299. *The Hydrothermal Chemistry of Silicates. Part III.* Reactions of Analcite and Leucite.*

By R. M. BARRER, L. HINDS, and E. A. WHITE.

Because of the readiness with which it may be synthesised (Part II) analcite ($Na_2O,Al_2O_3,4SiO_2,2H_2O$) has been used as a starting point for preparation, in high yield, of minerals and mineral-type compounds under reproducible and relatively accessible conditions. Analcite (or leucite, $K_2O,Al_2O_3,4SiO_2$) has been converted hydrothermally into nepheline, cancrinite, nosean, sodalite, barium felspar, potash felspar, kaliophilite, kalsilite, hieratite, α-eucryptite, and various species without naturally occurring counterparts. These include, *inter al.*, a lithium zeolite, $Li_2O,Al_2O_3,2SiO_2,4H_2O$, described in Part I, a zeolitic compound, $K_2O,Al_2O_3,3SiO_2,3H_2O$, and four mineral-type compounds containing intercalated potassium chloride or bromide, and barium chloride or bromide. The salt could usually be extracted hydrothermally, sometimes with recrystallisation. Conditions of formation, and optical and *X*-ray data, of these and other species have been given.

Many of the metamorphoses of analcite and leucite can be reversed under different conditions, so that various two-way reaction paths between these minerals and other species can be realised. Such paths have significance for the chemistry of zeolite and of granite formation and in the paragenesis of rock and soil-forming minerals.

ANALCITE, $Na_2O,Al_2O_3,4SiO_2,2H_2O$, is readily synthesised in quantity and in high purity (Barrer, *Discuss. Faraday Soc.*, 1948, No. 5, 326; Barrer and White, Part II *).

* Part II, *J.*, 1952, 1561.

It therefore provides a reproducible laboratory starting point for the study of further reactions of chemical and geochemical interest. It is as stable as most aluminosilicates, especially under mildly alkaline hydrothermal conditions, and shows both the sorptive and the ion-exchange properties of a normal zeolite. It can be converted by exchange of sodium for potassium into the felspathoid leucite, $K_2O,Al_2O_3,4SiO_2$. This and other cation-exchange reactions have been studied elsewhere and show that analcite has ion-sieve as well as molecular-sieve properties (Barrer, *J.*, 1950, 2342). Despite the stability of the analcite type of framework it has been found that simple ion-exchange, under appropriate and often specific reaction conditions, can give place to complete recrystallisation (cf. Barrer, *J.*, 1948, 127). This earlier work is now extended and many new hydrothermal recrystallisation reactions are described. One may indeed obtain from analcite a notable variety of aluminosilicates, some representative of important mineral groups and others not identified with naturally occurring species.

Experimental

Analcite was synthesised from gels of composition $Na_2O,Al_2O_3,4SiO_2$ + aq. in the presence of a slight excess of sodium hydroxide. Crystallisation was effected at 180° in an autoclave of internal capacity about 1 l. 100-G. lots of high purity were formed under these conditions, although at higher temperatures in presence of 5N-sodium hydroxide the product consisted only of cancrinite with excess of silica and sodium silicate crystals (Part II).

Leucite was prepared from analcite by heating the latter with concentrated potassium chloride solution at 200°. Several treatments were given, all of 24 hours' duration and with a fresh supply of potassium chloride each time :

$$NaAlSi_2O_6,H_2O + K^+ aq. = KAlSi_2O_6 + Na^+ aq. + H_2O$$

Samples of analcite or leucite were then heated at temperatures in the range 110—450° with various mineralising solutions. These included salts of lithium (Cl^-, NO_3^-, SO_4^{2-}), sodium (OH^-, Cl^-, CO_3^{2-}, SO_4^{2-}, SeO_4^{2-}), potassium (OH^-, CO_3^{2-}, F^-, Cl^-, Br^-, I^-, SO_4^{2-}, NO_3^-), rubidium (Cl^-), thallium (Cl^-), lead (Cl^-), and barium (Cl^-, Br^-). The stainless-steel autoclaves and the heating methods used have been previously described (Barrer and White, Part I, *J.*, 1951, 1167). Where possible, " AnalaR " salts were employed.

The crystalline products were thoroughly washed, and after being dried in air, were examined by optical and *X*-ray methods. Chemical analyses were carried out only where approximately 100% yields were obtained.

Results

Table 1 summarises the crystalline species obtained from analcite and leucite. For convenience the products are designated alphabetically. Among compounds of known composition it can be seen that the $Al_2O_3 : SiO_2$ ratio of 1 : 4 in the parent compound usually takes values 1 : 6, 1 : 4, and 1 : 2 in the metamorphic species. Where a change occurs from the ratio 1 : 4 in analcite and leucite, it is more usual to find silica rejected than alumina, so that the $Al_2O_3 : SiO_2$ ratio then decreases in the crystalline products. Reaction media were mostly on the alkaline side.

In the following sections we will describe the reactions of analcite with several types of salt, and will outline the properties of the metamorphic products.

Reactions with Carbonates.—Table 2 gives some results obtained, with sodium and potassium carbonate solutions as mineralisers. In all tables the symbols α, 2α, 3α, etc., denote respectively one, two, and three g. of analcite, and λ, 2λ, etc., denote similar weights of leucite. Where excess of salt is referred to it is understood throughout this paper that water is also present, but that the amount of salt is sufficient to give a saturated solution together with solid salt.

The cancrinites of Table 2 were identical with those synthesised from sodium aluminosilicate gels (Part II) and with those grown from hydroxide solutions (Table 3). The crystals usually appeared as thin hexagonal rods up to 50 μ long, with a mean $n = 1{\cdot}51$. *X*-Ray and optical data for cancrinite have been discussed in Part II. The yield of cancrinite from analcite improved with rising temperature, giving 100% conversion at 450°. As the yield grew, the crystal size often showed a parallel increase.

Kalsilite (Plate I) grew as small hexagonal plates ~25 μ across, although in treatments with KOH aq. crystals up to 250 μ were obtained. The mineral was in all respects identical with natural kalsilite, and gave $\varepsilon = 1{\cdot}534$, $\omega = 1{\cdot}541$. Complete conversion into kalsilite was

observed at 450°. Details of the formation of potash felspar from analcite have been given elsewhere (Barrer and Hinds, *Nature*, 1950, **166**, 562). *X*-Ray, optical data, and crystal habit are close to those for natural orthoclase (Table 8).

TABLE 1. *Alteration products from analcite and leucite.*

Species	Ref. letter	Probable ideal oxide formula
Cancrinite	A	$3(Na_2O,Al_2O_3,2SiO_2)X$ *
Nosean	B	$3(Na_2O,Al_2O_3,2SiO_2)X$ *
Sodalite	C	$3(Na_2O,Al_2O_3,2SiO_2)X$ *
Leucite	D	$K_2O,Al_2O_3,4SiO_2$
Kalsilite	E	$K_2O,Al_2O_3,2SiO_2$
Potash felspar	F	$K_2O,Al_2O_3,6SiO_2$
Kaliophilite	G	$K_2O,Al_2O_3,2SiO_2$
Nepheline	H	$(Na,K)_2O,Al_2O_3,2SiO_2$
Hieratite	I	K_2SiF_6
New species	J	Na,K aluminosilicate
Lithium zeolite	K	$Li_2O,Al_2O_3,2SiO_2,4H_2O$
α-Eucryptite	L	$Li_2O,Al_2O_3,2SiO_2$
New species	M	$K_2O,Al_2O_3,3SiO_2,3H_2O$
Potassium halide aluminosilicates	N	$K_2O,Al_2O_3,4SiO_2,x$KCl †
	O	$K_2O,Al_2O_3,4SiO_2,x$KBr †
Barium halide aluminosilicates	P	$BaO,Al_2O_3,4SiO_2,yBaCl_2,zH_2O$ ‡
	Q	$BaO,Al_2O_3,4SiO_2,yBaBr_2,zH_2O$ ‡
New species	R	Ba aluminosilicate
New species	S	Pb aluminosilicate
Barium felspar	T	$BaO,Al_2O_3,2SiO_2$
Near harmotome	U	$BaO,Al_2O_3,5SiO_2,6H_2O$(?)

* In these experiments X = (mNaOH + $n$$H_2O$), Na_2CO_3, or Na_2SeO_4 for cancrinite; 2NaCl for sodalite; and (mNaOH + $n$$H_2O$) or Na_2SO_4 for nosean (see Part II for explanation of m and n).

† A small amount of Na^+ is probably present. The value of x is ~ 2.

‡ A small amount of Na^+ is probably present. y and z may vary, depending on conditions of formation. Representative values are $y \sim \frac{2}{3}$, $z \sim 2$ (Barrer, *J.*, 1948, 127).

TABLE 2. *Reactions with carbonates.*

Reaction mixture	Time (days)	Temp. (c)	Product
2α + 10 c.c. 2N-Na_2CO_3	4	260°	Analcite + little *cancrinite*
,, ,,	4	300	Analcite + more *cancrinite*
,, ,,	4	360	Analcite + moderate *cancrinite*
,, ,,	4	410	Good yield *cancrinite*
2α + 10 c.c. 8N-Na_2CO_3	4	450	*Cancrinite* only
3α + 10 c.c. 5N-K_2CO_3	1	280	*Leucite*
,, ,,	1	360	*Leucite* + some *potash felspar*
2α + excess K_2CO_3 + 1 g. KOH + 10 c.c. H_2O	2	220	*Leucite* + some *kalsilite*
2α + 10 c.c. 8N-K_2CO_3	4	450	*Kalsilite* only
λ + sat. (K_2CO_3 + Na_2CO_3) aq.	14	110	Some *species J*
,, ,, ,,	14	110	,, ,,
,, ,, ,,	3	160	Good yield of *species J*
,, ,, ,,	7	160	,, ,,
,, ,, ,,	7	180	,, ,,
,, ,, ,,	0·67	195	~95% Conversion into *potash felspar*
,, ,, ,,	0·67	200	Smaller yield of *potash felspar*
λ + sat. K_2CO_3 aq.	3	160	No recrystallisation
,, ,,	7	160	,, ,,
,, ,,	3	200	,, ,,

Species J was found as small rectangular or sometimes rhombohedral tablets up to ~20 μ in length. They belonged to the monoclinic system, exhibiting considerable birefringence in some orientations; $\alpha = 1{\cdot}532$, $\beta = 1{\cdot}501$, $\gamma = 1{\cdot}495$. The compound was grown also in the presence of mixed sodium and potassium fluoride solutions (Table 4). Since it did not usually appear in major yield analytical data were not obtained. It could not be identified with any minerals and may be a new sodium–potassium aluminosilicate.

Reactions with Hydroxides.—In Table 3 reactions observed between hydroxide solutions and analcite or leucite are summarised. Both nosean and cancrinite were formed from analcite at 450°. In general, nosean was obtained only when the mineralising solution was very highly alkaline (~4N-NaOH). The products are the " basic " nosean and cancrinite described in Part II and then grown from gels. The introduction of potassium into the mineralising solution resulted at first in the formation of nepheline, but as the potassium content increased the yield

PLATE I.

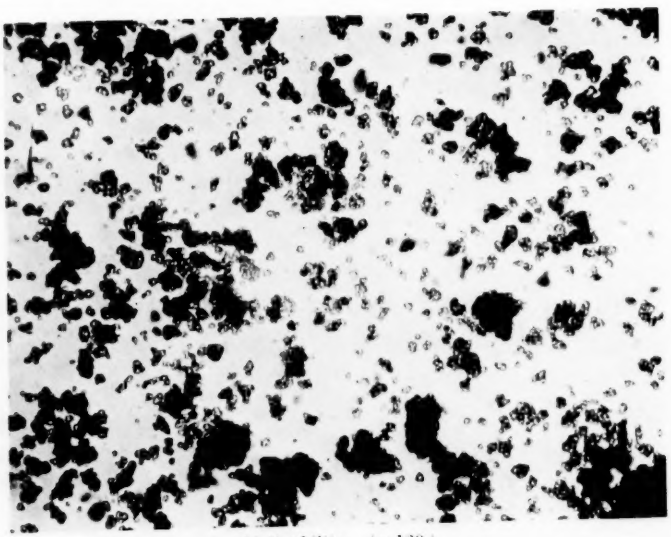
Kalsilite. (×120.)

PLATE II.

Nepheline (grown in presence of K^+*).* (×75.)

[*To face p.* 1468.

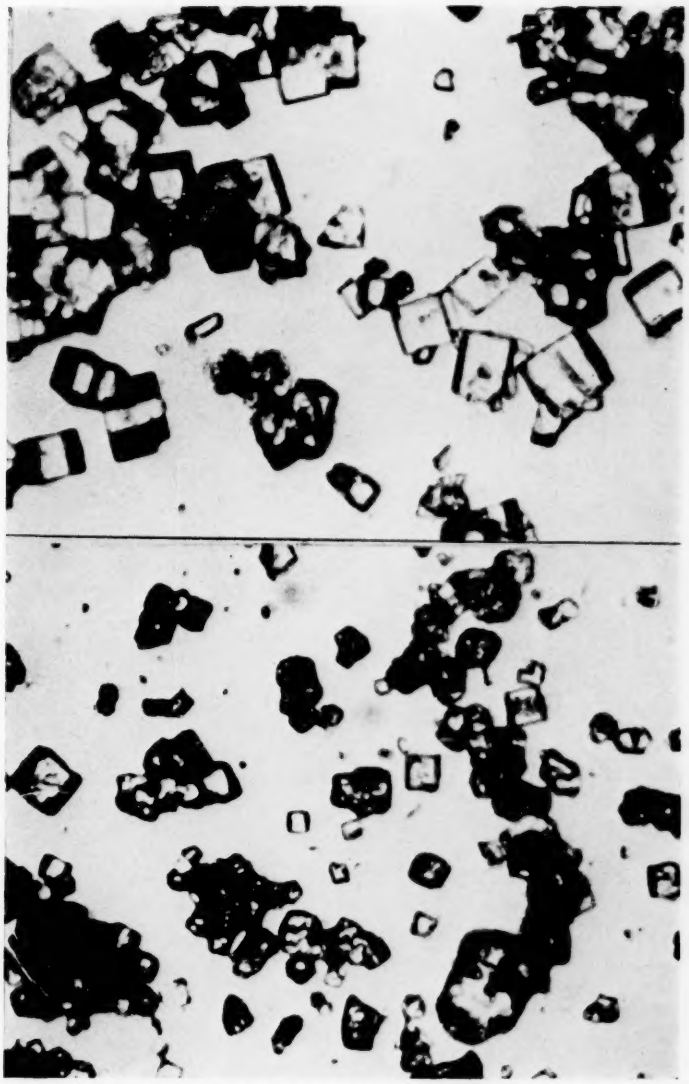
PLATE III.



Kaliophilite. (×120.)

PLATE IV.

Species M *obtained by hydrothermal treatment of compounds* N *and* O. (×120.)



Species P (*below*) *and* O (*above*). (×475.)

PLATE VI

Species R. (×75.)

PLATE VII.

Compound S. (×250.)

of nepheline diminished and at a ratio NaOH : KOH = 1 : 5 (by wt.) in the solution the product consisted mainly of kalsilite. The nosean and cancrinite were identical with the same species grown from gels (Part II).

The nepheline grew as hexagonal tablets as much as 400 μ wide (Plate II). They belonged to the hexagonal system with $\varepsilon = 1{\cdot}541$ and $\omega = 1{\cdot}545$, the *X*-ray powder photographs being indistinguishable from that of natural nepheline. It is interesting that nepheline grown in the presence of potassium differs somewhat in *n*, habit, and *X*-ray powder photographs from nepheline grown from sodium aluminosilicate gels (Part II). Although nepheline can contain potassium, continuous replacement of sodium by potassium over the whole range $NaAlSiO_4$ to $KAlSiO_4$ with retention of the nepheline structure did not often occur. Especially at higher

TABLE 3. *Reactions with hydroxides.*

Reaction mixture	Time (days)	Temp. (c)	Products
2α + 15 c.c. 2N-NaOH	2	330°	*Cancrinite* and some analcite
,, ,,	2	360	*Cancrinite* and little analcite
2α + 10 c.c. 3N-NaOH	2	360	*Cancrinite* only
,, ,,	4	450	*Cancrinite* 100%. Large crystals
2α + 10 c.c. 5N-NaOH	4	450	*Nosean* only
2α + 1 g. NaOH + 0·2 g. KOH + 10 c.c. H_2O	2	450	Large *nepheline* crystals only
2α + 0·6 g. NaOH + 0·6 g. KOH + 10 c.c. H_2O	2	450	,, ,, ,,
2α + 0·2 g. NaOH + 1·0 g. KOH + 10 c.c. H_2O	2	450	*Kalsilite* and some *nepheline*
λ + 10 c.c. N/100-KOH	4	190	Leucite unchanged
λ + 10 c.c. N/10-KOH	2·5	200	,, ,,
λ + 10 c.c. N/4-KOH	2	200	Leucite and some *species M*
½λ + 6 c.c. N/2-KOH	2	200	,, ,, ,,
½λ + 6 c.c. N-KOH	2	200	,, ,, ,,
½λ + 5 c.c. 2N-KOH	2	200	Good yield of *species M*, some *kaliophilite* and little leucite
½λ + 5 c.c. 3·6N-KOH	2	206	Excellent yield *kaliophilite*
½λ + 5 c.c. 5N-KOH	2	206	
½λ + 5 c.c. 3N-KOH	2	250	*Kalsilite* only
½λ + 5 c.c. 4N-KOH	2	250	,, ,,
¼λ + 5 c.c. 5N-KOH	2	250	Much leucite and some *species M* (autoclave leaked)
2λ + 10 c.c. 3N-KOH	2	350	*Kalsilite* only
,, ,,	2	400	,, ,,
2λ + 10 c.c. 5N-KOH	1	450	,, ,,

temperatures one observed instead the precipitation of nepheline and kalsilite together from potassium-rich mixtures.

Kaliophilite has the composition of potassium nepheline and was at low temperatures sometimes obtained as very small laminar crystals of indefinite outline and about 5 μ diameter (Plate III). The mean value of *n* was $1{\cdot}54_1$, and birefringence was low. The crystals gave *X*-ray data in agreement with those in the " Alphabetical Index of *X*-ray Data " (American Society for Testing Materials), although minor differences in intensity and spacing were also noted (Table 8).

Dilute solutions of potassium hydroxide (<N/4) at low temperatures (~200°) had little effect upon leucite, although isolated rectangular prisms of species M were observed. The yield at 200° increased with potassium hydroxide concentration, although some kaliophilite was also formed. Above 250° kaliophilite and species M gave place to kalsilite. The compound M was on occasions found as one layer of a zoned crystal consisting of inner and outer prisms. The mean refractive index of the outer layer (compound M) was 1·496. The system may be orthorhombic or tetragonal, but no complete indexing of the *X*-ray spacings for a tetragonal unit cell was obtained. Species M was also found as an alteration product after extraction of compounds N and O hydrothermally; (Plate IV); and again as very much finer elongated crystallites when gels $K_2O,Al_2O_3,3SiO_2$ were treated hydrothermally with excess of potassium hydroxide (unpublished work by R. M. Barrer and J. W. Baynham). The crystals grown from gels were sometimes in high yield, and analysis then gave the formula $K_2O,Al_2O_3,3SiO_2,3H_2O$. The mineral was zeolitic and when outgassed could sorb ammonia at 200°. *X*-Ray spacings are given in Table 8 and further determinations of refractive index gave $\varepsilon = 1{\cdot}490$ and $\omega = 1{\cdot}494$. The compound could not be identified with any natural zeolite such as thomsonite, natrolite, or scolecite, or with any potassium aluminosilicate.

Reactions with Halides.—The mineralising action of fluorides, chlorides, and bromides has

now been studied in some detail, using analcite, leucite and, as reported earlier, aluminosilicate gels (Barrer, *J.*, 1948, **127**). The present work is in part an extension of that carried out previously, and the experiments are summarised in Table 4. Hieratite, species J, α-eucryptite, and one of the lithium zeolites of Part I were all identified by *X*-ray photography, and kalsilite was identified optically.

Among conversions in which fluorides were used it was noteworthy that mixed NaF–KF solutions are more effective than either salt alone (cf. p. **1474**). Hieratite was not formed above 300°, probably being too soluble for deposition above this temperature. The crystals were small (~5 mμ) and isotropic.

TABLE 4.

Reaction mixture	Time (days)	Temp. (° c)	Products
Reactions with fluorides.			
4α + 6 g. KF + 7 c.c. H_2O	2	250	*Hieratite* with *leucite*
2α + 4 g. KF + 7 c.c. H_2O	2	350	*Kalsilite* with *leucite*
,, ,, ,,	2	450	,, ,,
α + excess (Na,K)F	14	110	*Hieratite* and *species J*
λ + excess (Na,K)F	1	200	*Hieratite* and less of *species J*
Reactions with chlorides.			
α + excess LiCl	4	220	Li-*zeolite* ($Li_2O,Al_2O_3,2SiO_2,4H_2O$) and analcite
α + excess NaCl	2	360	Unaltered analcite
,, ,,	3	400	Analcite and some *sodalite*
,, ,,	4	450	*Sodalite*
α + excess NaCl + 10 c.c. 2N-NaOH	4	350	,,
2α + 1—6 g. KCl + 5 c.c. H_2O *	4	360	*Leucite* and some *species N*
2α + 1—6 g. KCl + 10 c.c. H_2O *	4	360	
2α + 1—4 g. KCl + 15 c.c. H_2O *	4	360	
2α + 4 g. KCl + 7 c.c. H_2O	2	400	*Leucite* and more *species N*
,, ,, ,,	2	450	*Leucite* and better yield *species N*
½α + excess RbCl	1	360	Rb-analcite
½α + excess TlCl	1	360	Tl-analcite
2α + excess (Na,K)Cl	2	450	Mainly *sodalite* (containing some K)
α + excess $PbCl_2$	7	400	Mainly *species S*
α + excess $BaCl_2$ †	2—4	~200	*Species P* (yield decreasing with increasing H_2O in mixture)
3·4α + 10 g. $BaCl_2$ + 15 c.c. H_2O	2	225	*Species P* and little analcite
2λ + 8 g. $BaCl_2$ + 10 c.c. H_2O	2	220	*Species P*
α + excess $BaCl_2$ ‡	2	350	
,, ,,	2	400	*Species P*, very small crystals
,, ,,	2	450	
Reactions with bromides.			
2α + excess KBr + 5—15 c.c. H_2O †	4	200—250	Some conversion into *species O*
2α + 6 g. KBr + 7 c.c. H_2O	4	300	*Species O* in higher yield
,, ,, ,,	1	360	Very good yield *species O*. Trace of *kalsilite*
,, ,, ,,	1	400	
,, ,, ,,	1	450	Excellent yield *species O*
α + excess $BaBr_2$ †	2—3	194—209	*Species Q*; yield increases as amount of H_2O decreases
3·4α + 10 g. $BaBr_2$ + 15 c.c. H_2O	3	225	*Species Q*; excellent yield
2α + excess $BaBr_2$	2	350	*Species Q*; crystals small
,, ,,	2	400	
,, ,,	2	450	*Species Q*; few large crystals of *species R*

* Results of a series of experiments. † Results of a series of experiments in which proportions of solids and water were varied (Barrer, *J.*, 1948, 127). ‡ Six treatments of α with excess of $BaCl_2$ at 210° gave *species P* only.

The compounds N, O, P, and Q (see Plate V for P and O) had been prepared by Barrer (*J.*, 1948, **127**), N and O in minor, and P and Q in major yields. We have now obtained high yields of N and O, extended the range of conditions for forming all the species, and characterised them more fully. The formation of species N and O proceeded only to a very limited extent at 250° and the yield did not vary much with changing proportions of analcite, potassium chloride or bromide, and water. Repeated treatments with fresh charges of chloride or bromide also failed to give noticeably increased yields. It seems likely that the leucite which is also formed by ion-exchange during the first treatment with the potassium salts is then stable at 250° and that Na^+

in the analcite lattice is necessary for reaction. On the other hand treatment of analcite with a 1 : 1 mixture of sodium and potassium chlorides produced a partly ion-exchanged sodalite. Yields of species N never exceeded about 25%, but compound O was obtained in major yield at 450°. Species N was, however, obtained in higher yield by direct synthesis (Table 6).

Reactions of Analcite with Miscellaneous Salts.—Salts other than hydroxides, carbonates, chlorides, and bromides were sometimes very successful mineralisers (Table 5). Reaction

TABLE 5.

Reaction mixtures	Time (days)	Temp. (c)	Products
α + excess KNO_3 + little H_2O	1	360°	*Leucite*
α + excess $LiNO_3$ + 10 c.c. H_2O	2½	250	Analcite and Li-*zeolite* ($Li_2O,Al_2O_3,2SiO_2,4H_2O$)
α + excess $LiNO_3$ + 8 c.c. H_2O	3	270	Li-*zeolite* in high yield
α + excess $LiNO_3$ + 7 c.c. H_2O	6	310	α-*Eucryptite* and Li-*zeolite*
4α + 8 g. KNO_3 + 8 c.c. H_2O	2	250	*Leucite*
α + excess Na_2SO_4 + little H_2O	1	360	Analcite
α + excess Na_2SO_4 + 2N-NaOH	1	360	Analcite; some alteration
2α + excess Na_2S + little H_2O	3	400	*Sodalite* as large crystals
α + excess Na_2SeO_4 + 5 c.c. N-NaOH	2	360	*Cancrinite*
2α + 4 g. K_2SO_4 + 7 c.c. H_2O	3	400	*Leucite*

products obtained with $LiNO_3$ aq. (α-eucryptite and the zeolite $Li_2O,Al_2O_3,2SiO_2,4H_2O$) were also obtained by using LiCl aq. (Table 4) and by direct synthesis (Part I). The sodalite, prepared as 0·5-mm. crystals by using sodium sulphide aq., was identical with the " basic " sodalite of Part II. There was no evidence of occlusion of sodium sulphide in the lattice. The cancrinite formed by use of alkaline sodium selenate solution gave an *X*-ray pattern indistinguishable from that of a natural sulphatic cancrinite. " Basic " cancrinites prepared as in Part II showed various minor differences in the *X*-ray photographs from sulphatic cancrinite. Thus the identity between the selenatic and sulphatic cancrinite may result from intercalation, not of sodium hydroxide, but of sodium selenate in place of sodium sulphate. Qualitative analysis of the selenatic cancrinite showed the presence of considerable selenium in the mineral.

Some Properties of the Mineral-type Compounds N, O, P, *and* Q.—The results shown in Table 4 and Barrer's earlier experiments (*J.*, 1948, 127) show that the species N, O, P, and Q are readily formed in presence of potassium chloride or bromide, or barium chloride or bromide from analcite or leucite. The compounds P and Q were also grown by Barrer from gels with addition of excess of barium chloride or bromide and some water. The experiments summarised in Table 6 show that N and O may be grown in like manner from gels of composition $Al_2O_3,4SiO_2$, when treated with excess of potassium chloride or bromide in presence of potassium hydroxide solution.

The cubic crystals obtained in presence of potassium fluoride (Table 6) were shown from *X*-ray photographs to be of the same type as species N (or O). Hieratite (K_2SiF_6) obtained

TABLE 6. *Direct hydrothermal synthesis of* N *and* O *from gels.*

Reaction mixture : 2 g. of gel plus	Time (days)	Temp. (c)	Products
0·6 g. KOH + excess KCl	2	300°	Some *species N*, much *kalsilite*
0·5 g. KOH + 0·1 g. NaOH + excess KCl	1	400	*Kalsilite*
0·5 g. KOH + excess KCl	1	450	Moderate yield of N
0·2 g. KOH + excess KBr	1	360	Some *species O*, mainly *leucite*, and *kalsilite*
0·6 g. KOH + excess KBr	1	400	Mainly *species O*, some *kalsilite*
0·6 g. KOH + 0·5 g. KF	1	360	*Cubic crystals* like N, and some *leucite*
0·6 g. KOH + 1 g. KF	1	400	*Cubic crystals* like N, and some *kalsilite*

at lower temperatures from analcite or leucite in presence of potassium fluoride (Table 4) was not precipitated above 300°. Table 6 also shows that species N and O were frequently less in amount than *kalsilite* or *leucite*. Wyart (*Discuss. Faraday Soc.*, 1949, **5**, 324) has reported a difficulty in obtaining leucite by hydrothermal reaction.

In Barrer's earlier work (*J.*, 1948, 127) it was suggested that the compounds, N, O, P, and Q were all based upon one aluminosilicate framework. This was shown to be true of P and Q, but the substances N and O could not then be obtained in large enough yield for adequate *X*-ray study. Considerable amounts of both phases have now been prepared and it has been

found that, while N and O are based upon a single aluminosilicate framework, this is not identical with the framework characteristics of P and Q (see Table 8).

The crystals of N and O grew as well-defined cubes, showing moderate birefringence normal to all faces. They were orthorhombic, with $\alpha = 1{\cdot}525$, $\beta = 1{\cdot}523$, and $\gamma = 1{\cdot}518$ for species N; $\alpha = 1{\cdot}542$, $\beta = 1{\cdot}539$, and $\gamma = 1{\cdot}534$ for species O, although small variations from these values were sometimes noted. Optimum yields were obtained at 450°, at which temperature yields of compound O reached 100%. Individual crystals measured as much as 200 μ along the cube edge.

Both N and O when treated with water at 250° for a day recrystallised to a mixture containing orthoclase, leucite, and as principal species large prismatic crystals of compound M. Hydrothermal extraction of species O at 170° removed potassium bromide, at first without lattice collapse or recrystallisation but with progressive decreases in refractive index. After 4—5 extractions, each of a day, the amount of potassium bromide removed at 170° became very small. The mother-liquors during the first extractions were extremely alkaline (pH ~14). This extracted material was outgassed but then proved inert as a sorbent towards ethane at −78° and to ammonia at 0°. It was thus contrasted with the extracted pseudomorph of compound P (Barrer and Riley, *J.*, 1948, 133). Attempts to remove potassium bromide from O by percolation at 100° were not successful, but treatment with saturated aqueous silver nitrate at 120° gave a Ag^+ ion-exchanged form having a mean value of $n = \sim 1{\cdot}69$.

Compounds P and Q grew as small isotropic cubes of $n = 1{\cdot}587$ for P and 1·597 for Q, although variations were noted between different preparations. The best crystals were formed at about 220°. Although good yields (as shown by *X*-ray photography) were obtained up to 450° the crystals became very small above 300°. The crystals belonged to the cubic system, the unit cell edge being $13{\cdot}2_0$ Å for P and $13{\cdot}2_8$ Å for Q.

Hydrothermal extraction of compound P at ~200° gives a yield of gas-sorbing zeolitic crystals pseudomorphic with P, together with some recrystallisation (Barrer, *J.*, 1948, 127). Extraction has now been followed by *X*-ray photography. The mineral Q (containing barium bromide) showed a greater tendency to recrystallise, giving after thirteen extractions of one day each at 220°, a good yield of species U (see below, also Table 8 and Barrer, *J.*, 1948, 127, Plate 6). At 250° one hydrothermal extraction of P gave a slight lattice shrinkage only; but after the sixth extraction recrystallisation to species T (see below and Table 8) was extensive.

Both compounds P and Q showed ion-exchange properties. The silver forms were obtained by treatment with saturated aqueous silver nitrate at 120°, and the ammonium form by heating with ammonium chloride vapour at 330°. Unlike species N and O the silver ion-exchanged form has a refractive index close to that of the original phase (~1·59), although changes in the *X*-ray powder photographs were observed. The effect of thermal treatment of the crystals was

TABLE 7. *Comparison of three types of synthetic aluminosilicate.*

Property	Species N & O	Species P & Q	Synthetic sodalite-nosean crystals
Crystal system	Orthorhombic	Cubic	Cubic
Crystal habit	Cuboids	Cubes	Rhombic dodecahedra
Ion-exchange	Yes	Yes	Yes
Intercalated salts	KF, KCl, KBr	$BaCl_2$, $BaBr_2$	NaCl, Na_2SO_4, NaOH, etc.
Probable formula	$(Na,K_2)_2O,Al_2O_3,4SiO_2$, 2KX	$(Na_2,Ba)O,Al_2O_3,4SiO_2$, $0{\cdot}67BaX_2,2—3H_2O$ *	$3(Na_2O,Al_2O_3,2SiO_2)$, 2NaCl
Crystallisation from gels	Yes	Yes	Yes
Thermal stability	Stable to >550°	Stable to >550°	Stable to >550°
X-Ray pattern	Phases containing KCl and KBr show same spacings	Small but definite expansion of phase containing $BaBr_2$ compared with that containing $BaCl_2$	Range of structures possible between noseans and sodalites (Part II)
Crystal chemical nature	All are robust three-dimensional aluminosilicate framework structures		
Hydrothermal extraction at 200°	Removes intercalated salt; extensive recrystallisation	Removes intercalated salt; less recrystallisation	No extraction without decomp.
Sorptive properties of crystals when extracted	Not a general sorbent	Excellent molecular sieve sorbent †	Non-sorbent

* There is some evidence of variable halide and water content (Barrer, *J.*, 1948, 127).
† Sorptive properties have been studied by Barrer and Riley (*J.*, 1948, 133).

TABLE 8. *Summary of principal* X-*ray spacings* (Å).

Synthetic potash felspar		Natural ortho-clase		Species T		Species S		Synthetic kalsilite		Synthetic kalio-philite		Natural kalio-philite*	
d	*I*	*d*	*I*	*d*	*I*	*d*	*I*	*d*	*I*	*d*	*I*	*d*	*I*
6·69	vvw	6·38	m	6·5	m	14	vs	4·36	mw	6·22	ms	—	—
6·00	vw	—	—	—	—	7·5	m	3·97	s	4·49	mw	—	—
5·55	vw	5·60	mw	—	—	6·2	m	3·11	vvs	4·24	m	4·24	40
4·65	w	4·64	mw	4·63	vvw	4·25	s	2·58	vs	3·99	m	3·92	40
4·26	m	4·20	s	—	—	3·80	s	2·47	w	—	—	3·72	40
3·97	m	4·00	w	3·99	s	3·60	m	2·43	vw	—	—	3·46	40
3·78	m	3·80	ms	3·78	s	3·31	m	2·22	w	—	—	3·40	60
3·68	vw	3·66	ms	3·60	mw	3·21	mw	2·17	m	3·07	vvs	2·86	100
3·47	ms	3·47	s	3·47	mw	3·10	vw	1·98$_5$	vw	2·82	w	2·79	40
3·31	vs	3·35	vw	} 3·29	vvs	3·00	vs	1·95$_0$	vvw	—	—	2·69	40
3·25	vs	3·25	vvs	}		2·89	w	1·93$_0$	vvw	2·68	vvw	2·59	20
3·10	w	—	—	—	—	2·76	w	1·76$_9$	vw	2·60	s	2·50	80
3·00	mw	2·99	m	} 2·97	vvs	2·69	vw	1·65$_9$	mw	2·49	m	2·45	40
2·92	mw	2·90	m	}		2·64	w	1·62$_1$	mw	—	—	2·41	20
2·76	vw	2·76	mw	2·76	mw	2·48	(diff.) mw	1·57$_3$	m	—	—	2·39	20
2·68	vw	—	—	—	—	2·39	vvw	1·55$_7$	vw	2·39	mw	2·34	20
2·59	mw	2·60	mw	2·58	s	2·27	vvw	1·49$_0$	m	—	—	2·24	20
—	—	2·53	mw	—	—	2·22$_6$	vvw	1·46$_1$	vw	2·26	w	2·21	20
—	—	2·42	w	—	—	2·14$_8$	vvw	1·373	vw	—	—	2·18	40
2·31	vvw	2·33	vw	2·38	(diff.) w	2·10$_6$	vvw	1·332	vvw	2·21$_5$	vw	3·09	20
2·21	vw	2·23	vvw	—	—	2·06$_0$	mw	1·291	w	2·16$_6$	vvw	2·16	20
2·17	vw	2·15	m	2·21	(diff.) m	2·02$_2$	mw	1·265	mw	2·11$_1$	m	2·13	50
2·13	vw	2·11	vw	—	—	1·96$_5$	vvw	1·228	mw	2·05$_2$	w	2·06	20
2·03	vvw	2·04	vvw	2·07	vw	1·91$_5$	vvw	1·211	mw	1·98$_9$	vw	1·97	20
1·98	vvw	1·98	vw	—	—	1·85$_9$	vw	1·192	mw	1·91$_5$	mw	1·93	40
1·93	vvw	1·92	vw	—	—	1·79$_3$	vvw	1·138	vw	1·87$_0$	mw	1·86	20
1·88$_8$	vvw	1·90$_9$	vw	—	—	1·74$_2$	vvw			—	—	1·82	20
1·84$_7$	vvw	1·85$_3$	vw	1·85$_2$	w					—	—	1·80	20
1·79$_6$	mw	1·79$_7$	m	1·79$_9$	m					1·76$_0$	mw	1·76	40
				1·63$_3$	vvw					—	—	1·67	20
				1·58$_7$	w					1·67$_0$	m	1·65	60
				1·52$_9$	vvw								
				1·50$_3$	vw								

Species J		Species M		Species O †		Species P		Species Q		Species R		Species U	
d	*I*	*d*	*I*	*d*	*I*	*d*	*I*	*d*	*I*	*d*	*I*	*d*	*I*
6·27	mw	7·2	w	6·88	w	13·2	vs	13·3	vs	4·95	vw	9·7	w
5·22	ms	4·27	w	5·43	w	—	—	9·5	mw	4·01	vw	8·2	w
4·07	mw	3·28	vs	4·98	mw	—	—	6·0	w	3·53	ms	7·2	w
3·90	s	2·96	s	4·23	w	4·41	s	4·42	mw	3·33	m	6·5	ms
3·41	s	2·82	vw	3·92	w	4·17	m	4·20	mw	3·12	mw	5·11	ms
3·27	w	2·74	ms	3·77	w	4·00	w	4·00	w	2·88	m	4·49	vw
3·15	vvs	2·42	mw	3·62	w	3·81	ms	3·82	s	2·64	vvw	4·22	vw
3·00	mw	2·17	m	3·45	vs	3·63	vw	3·66	vvw	2·48	vs	4·10	vs
2·91	w	1·86$_5$	m	3·27	ms	3·50	vw	3·50	vw	2·23	vw	3·87	m
2·82	w	1·79$_3$	ms	3·06	vvs	3·33	w	3·33	w	2·11	vvw	3·66	mw
2·70	m	1·73$_0$	m	2·95	ms	3·20	m	3·20	vs	1·94$_9$	vvw	3·26	mw
2·62	w	1·67$_3$	m	2·80	ms	3·03	vs	3·04	vs	1·76$_0$	m	3·02	mw
2·48	mw	1·63$_5$	mw	2·71	m	2·92	vvw	—	—	1·70$_3$	w	2·85	m
2·37	w	1·59$_4$	mw	2·59	vvw	2·81	s	2·81	s	1·57$_6$	vvw	2·77	m
2·31	vw	1·48$_8$	mw	2·43	vw	—	—	2·64	ms	1·50$_3$	vvw	2·69	m
2·24	mw	1·28$_2$	vw	2·37	w	2·54	ms	2·54	m	1·43$_2$	vvw	2·59	w
2·20	mw	1·26$_4$	vw	2·29	mw	2·37	vvw	2·33	vw	1·40$_6$	vvw	2·48	w
2·13$_0$	vw			2·24	mw	2·30	m	2·30	ms	1·24$_8$	vvw	2·39	w
2·11$_0$	mw			2·17	vw	2·12$_3$	vvw	2·10$_8$	vvw	1·10$_7$	vvw		
2·02$_9$	w			2·12$_7$	vw	2·00$_5$	vvw	2·02$_4$	vvw				
1·95$_1$	w			2·08$_4$	w	1·79$_4$	vvw	—	—				
1·84$_0$	w			1·95$_4$	w	1·74$_6$	vw	1·74$_8$	w				
1·71$_8$	mw			1·91$_6$	w	1·69$_3$	vvw	1·69$_8$	vvw				
1·66$_5$	vvw			1·88$_2$	w	1·64$_9$	w	1·64$_9$	vw				
1·63$_7$	vw			1·83$_9$	w	1·61$_3$	vw	1·61$_0$	vw				
1·61$_3$	w			1·81$_2$	w	1·55$_6$	vw						
1·56$_6$	w			1·77$_9$	vvw	1·42$_6$	w						
1·52$_3$	vw			1·72$_6$	m	1·38$_5$	vw						
1·47$_9$	vw			1·67$_0$	vvw								
1·44$_1$	vw			1·62$_5$	vvw								
1·35$_7$	vw												

* Spacings from A.S.T.M. index.
† Species N is identical.

followed by *X*-ray studies up to 550°. No changes in the lattice could be detected, but water up to 6% (by weight) was evolved.

Analyses have shown that the compounds P and Q have somewhat variable halide and water content. From several analyses Barrer (*J.*, **1948**, **127**) adduced an ideal formula $BaO,Al_2O_3,4SiO_2,0{\cdot}67BaCl_2,2—3H_2O$ for the chlorine-containing phase.

It is of interest to compare the behaviour of N and O, of P and Q, and of synthetic sodalite–nosean minerals, because these three types of compound show certain resemblances (Table 7).

Compounds R, S, T, *and* U.—From Table 4 it is seen that hydrothermal treatment of analcite at 450° with excess of barium bromide produced a few crystals of the phase R. These grew as micaceous plates up to 1 mm. across (Plate VI). They were feebly birefringent, of straight extinction, and showed pleichroism, the colour varying between blue and purple. They gave a biaxial negative interference figure, the optic axial angle being very small, and they probably belonged to the monoclinic system. The mean value of n was ~1·67. A small amount of the pure substance was collected by sieving and hand-picking, and *X*-ray data were obtained (Table 8). The substance could not be identified with any barium aluminosilicate. Although yields were small, formation was reproducible.

During attempts to prepare lead analcite from analcite and lead chloride at temperatures between 250° and 400° the recrystallisation of part of the analcite was observed. Two metamorphic products appeared of which one, species S, was most abundant (Plate VII). *X*-Ray spacings of S are given in Table 8. The crystal habit recalls that of albite, and the spacings show a superficial resemblance to those of potash felspar, although there are some considerable differences also. Kohler (*Anz. Akad. Wien., Math.-naturw. Klasse*, 1935, **72**, 123) has made a synthetic lead felspar.

Crystals of species T appeared after the fifth extraction of compound P (prepared at 450°) with distilled water at 250° (*J.*, **1948**, **127**). *X*-Ray spacings in Table 8 show a correspondence with potash felspar sufficient to indicate that T belongs to the felspar group. It may be a celsian, but the crystals were too small for adequate optical characterisation. The mean refractive index of ~1·56 is lower than that of celsian. This may be due to the presence of some sodium in both P and T, derived from the parent mineral analcite.

Species U was derived principally from the compound Q, although it was also found as an alternative product from P (cf. Barrer, *J.*, **1948**, **127**, Fig. 6). It appeared as elongated prisms up to 150 μ long and often eroded. One specimen, when outgassed at ~330° and tested as a sorbent, still retained its characteristic *X*-ray spacings (Table 8). The powder photographs showed resemblances to, but some differences from, a natural harmotome. Species U gave a mean value of n ~1·517.

Discussion

In general, at low temperatures, leucite and analcite showed ion-exchange alone (Barrer, *J.*, 1950, 2342). Recrystallisations set in with saline solutions only at more elevated temperatures. Exceptions arise, however, with *mixed* sodium and potassium salt solutions. Thus potash feslpar was formed at 195—200° from leucite and saturated, mixed sodium and potassium carbonates (cf. Barrer and Hinds, *Nature*, 1950, **166**, 562). The aluminosilicate J was formed under similar conditions at 160°; and hieratite (K_2SiF_6) grew at temperatures as low as 110° with saturated, mixed sodium and potassium fluoride solutions as mineraliser. On the other hand in the presence of solutions of one of the carbonates alone recrystallisation required temperatures of at least 300°, and usually gave rise to different phases. These phenomena may be of general occurrence. If so, geologically significant low-temperature interconversions of minerals may be possible, because mixed solutions will be common under natural conditions. Knowledge of synthetic mineralogy may also be improved by investigating the hydrothermal growth of aluminosilicates from mixed gels. To a limited extent this has been attempted by Wyart and Mlle. Michel-Levy (*Compt. rend.*, 1949, **229**, 131) for the system $Na_xK_{1-x}AlSiO_4$ ($0 < x < 1$).

A notable feature of the aluminosilicate syntheses recorded in Parts I and II and this paper has been that slight but distinct structural and optical differences may arise between synthetic minerals and their naturally occurring counterparts (*e.g.*, potash felspar, kaliophilite, nepheline, albite, α-eucryptite). Such differences may be explained at least in part by the fact that the synthetic form is often a chemically pure end-member. Natural aluminosilicate crystals frequently contain, by isomorphous replacements,

appreciable amounts of other elements. Nepheline grown by us in presence of solutions containing both K^+ and Na^+ was, in accordance with this idea, indistinguishable from a natural nepheline, but differed slightly from the pure synthetic sodium nephelines.

The ease of formation and the persistence of analcite in the hydrothermal sodium aluminosilicate field has already been commented upon (Part II). In the present work it has been shown that analcite and leucite can in turn give high yields of various minerals (Table 1). To these may be added albite, formed from analcite by sintering (Part II) and kaolinite, made from analcite or leucite under somewhat acid conditions (Norton, *Amer. Min.*, 1941, **26**, 1; Schwarz and Trageser, *Z. anorg. Chem.*, 1933, **215**, 190). In their turn, however, many of these rock and soil-forming minerals can be re-converted by mineralising solutions at least in part into analcite. This is true of leucite, nepheline, potash felspar (adularia and microcline), albite, okenite, muscovite, eucryptite, and kaolin (Barrer, *J.*, 1950, 2342; von Nieuwenberg and Blumendahl, *Rec. Trav. chim.*, 1931, **50**, 989; Stevenson, *J. Geol.*, 1916, **24**, 180; Doelter, *Neues Jahrb. Miner.*, 1890, I, 118; Friedel, *Bull. Soc. Miner. franç.*, 1896, **19**, 5; Barrer and White, Part I; Lemberg, *Z. deut. geol. Ges.*, 1887, **39**, 559). Similar relations arise between leucite and other species, so that both analcite and leucite figure in a variety of two-way paths by which they may be generated from, or give rise to, diverse important species. Leucite has been reported as being formed from kaliophilite, kaolin, felspars, mica, and analcite (von Nieuwenberg and Blumendahl, *loc. cit.*; Lemberg, *loc. cit.*; Friedel and Friedel, *Bull. Soc. Miner. franç.*, 1890, **13**, 129; Barrer, *J.*, 1950, 2342). In turn it may give rise to analcite, orthoclase, kaolinite, and sericite (Barrer, *J.*, 1950, 2342; von Nieuwenberg and Blumendahl, Schwarz and Trageser, and Norton, *locc. cit.*). Leucite is a relatively common pyrolytic mineral, although its low-temperature hydrothermal synthesis has also been noted (cf. Table 6). Analcite is a hydrothermal mineral, but there is the possibility that it can be formed in deep-seated rocks as a primary mineral (Scott, *Trans. Geol. Soc., Glasgow*, 1916, **16**, 34; Yoder, *Amer. J. Sci.*, 1950, **248**, 312).

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300. *The S_N Mechanism in Aromatic Compounds. Part IV.**

By JOSEPH MILLER and VINCENT A. WILLIAMS.

ortho-Effects are shown to exhibit considerable variation in both magnitude and character. The lack of connection between geometrical and *ortho*-effects is clearly shown, and evidence is given for a field effect.

STERIC effects associated with *ortho*-substituents in aromatic compounds have been known for many years, and numerous references are quoted by Hughes (*Quart. Reviews*, 1948, **2**, 167). In the field of reactions being studied in this series, the papers of Spitzer and Wheland (*J. Amer. Chem. Soc.*, 1940, **62**, 2995) and of Berliner, Quinn, and Edgerton (*ibid.*, 1950, **72**, 5305) may be given as examples.

Differential effects between *ortho*- and *para*-positions may normally be neglected only in comparison with the larger differences usual between effects at these positions, and at the *meta*-positions. A substituent in the *ortho*-position may have superimposed on its normal polar behaviour a steric factor which usually reduces its effect as compared with the same substituent at the *para*-position (cf. de la Mare, *J.*, 1949, 2871). This applies even where a hydrogen atom is being replaced. With the more common replacement here of halogens or larger groups the effect is enhanced.

The normally less potent *I* effects act more strongly from the nearby *ortho*-positions, but the *T* (including both *M* and *E*) effects, where available, will be reduced. This is due

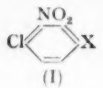
* Part III, *J.*, 1952, 3552.

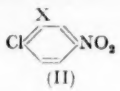
both to steric inhibition of conjugation of the group with the ring, and to the lesser delocalisation of the p or π electrons as compared with the same substituent at the *para*-position.

In the transition state of S_N2 reactions, the additional group bonded at the reactive centre normally enhances any steric hindrance (Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173); however, in the aromatic series only four groups are bonded in the transition state, and this is also associated with a change to a quinonoid type of structure, and thus there may be little or no enhancement, and in fact, where there is already considerable steric hindrance in the initial state, the formation of the transition state may cause a steric acceleration (cf. Ingold, *Nature*, 1951, **167**, 987; Beckwith, Miller, and Leahy, Part III *). Finally, the existence of a direct-charge field effect, absent in the *para*-position, may accelerate or retard a reaction according to the sign of the charge and electrical character of the reagent.

The work now described is intended to confirm these general differences between *ortho*- and *para*-substituents, to show that *ortho*-effects are mainly polar and not geometrical in origin, and in particular to show that *ortho*-effects may be accelerative as well as hindering.

The activating or deactivating power of substituents has been defined and measured in the form of substituent rate factors (Miller, *J.*, 1952, 3550). These correspond to the partial rate factors of aromatic electrophilic substitution (Ingold *et al.*, *J.*, 1927, 2918; 1931, 1959). The substituent rate factors, and the *para*/*ortho* ratios of these have been obtained by measurements in the mononitro-series (I and II) and dinitro-series (III and IV), X being the variable substituent.


(I)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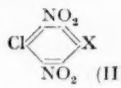
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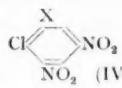
(IV)

In this general paper the substituents investigated are the same as in Part II (*loc. cit.*). Some measurements for *para*-substituents are repeated from that paper but most of the results are new. The rates of attack of sodium methoxide in dry methanol on 20 compounds are given in Table 1, which also includes the substituent rate factors at 50°, and activation energies (E) and frequency factors (as $\log_{10} B$).

The *para*/*ortho*-ratios of the substituent rate factors (a convenient name for which is "steric index") vary from 1 with zero *ortho*-effect to convenient numbers showing the magnitude and direction of the *ortho*-effects. Values less than 1 show accelerative, and above 1 hindering, influences. Similarly the ratios of the indices in the mononitro- and dinitro-series show the change in the effects.

Discussion of Results.—It is instructive to compare the actual *ortho*-effects with the simple geometrical hindrance. The latter is most simply given by the overlaps between the *ortho*-substituents and chlorine which would be present if all the substituents were in the plane of the ring : the overlaps with hydrogen are less important. The physical data used to obtain the overlaps are derived either from Archer's measurements (*Proc. Roy. Soc.*, 1947, *A*, **188**, 51) or from Pauling ("Nature of the Chemical Bond," 2nd Edn.). The radius of the amino-group was estimated as 1·82 Å, and the C=O distance, 1·24 Å, of the carbomethoxy-group is an arbitrary choice between values quoted for aldehydes and for acids.

Experimental and geometrical *ortho*-effects are compared in Table 2. The geometrical hindrance is in the order $Me > NO_2 > CO_2^- = CO_2Me > NH_2 > Cl$, all substituents exhibiting considerable interference. The order of ortho effects is : (*a*) in the mononitro-series $CO_2^- > CO_2Me > NO_2 > Cl$, (*b*) in the dinitro-series $CO_2^- > CO_2Me > NO_2 > NH_2^* > Cl^* > Me^*$. The direction of the effect is accelerative.

The extreme cases CH_3 and CO_2^- give a very convincing proof that geometrical hindrance is unimportant. The CO_2^- has less overlap than the methyl group. However, the steric index in the dinitro-series is 170·5 for the CO_2^- as against only 1·29 for the methyl group. In the mononitro-series it is 21·2 against an assumed value between 1 and 1·29.

Admitting a specific effect consequent on the ionic charge of the CO_2^- and substituting the carbomethoxy-group, one obtains an equally convincing comparison.

The $-I$, $-T$ groups by markedly denuding the point of attack of electrons, and by stabilising the *cyclo*pentadiene-type structure of the transition state, facilitate the approach

TABLE 1.

Compound *	10^5k_2 (temp. in parentheses)				10^5k_2 at 50°	Substituent	Substituent rate factor (H = 1)	E, kcal.	$\log_{10}B$
(i)	8·42 (71·0)	23·5 (81·6)	137 (100·8)	—	0·902	—	—	23·7	10·98
(ii)	3·62 (75·3)	6·82 (81·6)	37·45 (100·8)	—	0·260	—	—	23·5	10·30
(iii)	200 (0)	1060 (15·0)	2960 (25·0)	—	28,750	*p*-NO_2	$1·11 \times 10^5$	17·43	11·26
				—	—	*o*-NO_2	$3·19 \times 10^4$	—	—
(iv)	90·6 (26·35)	138 (30·2)	226 (35·0)	—	1,030	*o*-NO_2	$3·96 \times 10^3$	19·77	11·37
(v)	55·75 (30·2)	99·9 (34·8)	258 (45·3)	937 (59·9)	395	*p*-CO_2Me	$1·52 \times 10^3$	18·6	10·17
(vi)	99·75 (45·35)	322 (59·9)	1010 (75·3)	1560 (81·6)	147	*o*-CO_2Me	$1·63 \times 10^2$	17·04	8·69
(vii)	3610 (0)	6400 (5·2)	9170 (8·75)	—	355,300	*p*-CO_2Me	$3·45 \times 10^2$	16·1	11·43
(viii)	630 (−4·8)	1115 (0)	1955 (4·9)	—	154,300	*o*-CO_2Me	5·37	17·3	11·89
(ix)	4·85 (59·9)	20·45 (75·3)	36·4 (81·6)	165 (100·6)	1·96	*p*-CO_2^-	7·54	21·5	9·70
(x)	16·95 (81·6)	34·9 (87·8)	139 (100·8)	—	0·321	*o*-CO_2^-	$3·56 \times 10^{-1}$	28·6	13·87
(xi)	57·0 (0)	686 (26·1)	970 (30·2)	—	4,580	*p*-CO_2^-	4·45	15·17	8·91
(xii)	144 (35·15)	308 (41·85)	610 (48·05)	—	751	*o*-CO_2^-	$2·61 \times 10^{-2}$	22·02	12·77
(xiii)	18·6 (30·2)	79·2 (45·4)	343 (60·0	—	131	*p*-CH_3	$1·27 \times 10^{-1}$	19·20	10·08
(xiv)	114 (18·65)	260 (26·1)	402 (30·2)	650 (34·9)	2,820	*o*-CH_3	$9·81 \times 10^{-3}$	19·16	11·41
(xv)	23·8 (68·4)	30·4 (71·7)	86·0 (81·8)	418 (100·8)	3·61	*p*-Cl	$1·39 \times 10^1$	22·50	10·76
(xvi)	74·2 (69·9)	125 (75·6)	144 (77·2)	347 (87·1)	10·35	*o*-Cl	$1·15 \times 10^1$	21·90	10·80
(xvii)	51·8 (0)	546 (21·55)	762 (25·0)	—	7,360	*p*-Cl	7·15	17·37	10·61
(xviii)	743·5 (0)	1415 (4·55)	1590 (5·35)	2215 (9·05)	328,000	*o*-Cl	$1·14 \times 10^1$	21·36	14·97
(xix)	15·8 (81·8)	61·7 (100·1)	151 (112·6)	—	0·869	*p*-NH_2	$8·44 \times 10^{-4}$	20·40	8·73
(xx)	45·15 (41·25)	599 (69·9)	1100 (77·2)	1475 (81·6)	105·5	*o*-NH_2	$3·67 \times 10^{-3}$	19·58	10·26

(i) *p*-Chloronitrobenzene. (ii) *o*-Chloronitrobenzene. (iii) 1-Chloro-2 : 4-dinitrobenzene. (iv) 1-Chloro-2 : 6-dinitrobenzene. (v) Methyl 4-chloro-3-nitrobenzoate. (vi) Methyl 2-chloro-5-nitrobenzoate. (vii) Methyl 4-chloro-3 : 5-dinitrobenzoate. (viii) Methyl 2-chloro-3 : 5-dinitrobenzoate. (ix) 4-Chloro-3-nitrobenzoic acid. (x) 2-Chloro-5-nitrobenzoic acid. (xi) 4-Chloro-3 : 5-dinitrobenzoic acid. (xii) 2-Chloro-3 : 5-dinitrobenzoic acid. (xiii) 4-Chloro-3 : 5-dinitrotoluene. (xiv) 2-Chloro-3 : 5-dinitrotoluene. (xv) 2 : 5-Dichloronitrobenzene. (xvi) 3 : 4-Dichloronitrobenzene. (xvii) 1 : 4-Dichloro-2 : 6-dinitrobenzene. (xviii) 1 : 2-Dichloro-4 : 6-dinitrobenzene. (xix) 4-Chloro-3 : 5-dinitroaniline. (xx) 2-Chloro-3 : 5-dinitroaniline.

of the OMe group and lower the activation energy (E). This is shown by both the nitro- and the carbomethoxy-group. The *ortho*-effects when potent are associated with a much smaller fall in E, the difference being ascribed to repulsion by the oxygen atoms of these groups.

The CO_2^- group is of special interest. Although classified as a weakly activating $-I$, $-T$ group, it has available in the *ortho*-position only, a direct-field effect, opposite in sign and causing deactivation. The geometrical hindrance by this group is similar to that of the previous groups, but the repulsive effects are much stronger owing to the unit negative charge spread over two oxygen atoms. Very large steric indices are to be expected and

TABLE 2.

Substituent	Steric index : * (*a*) mononitro-series	(*b*) dinitro-series	Ratio of steric indices, *b*/*a*	Overlaps (Å) between *o*-substituent and Cl
NO_2	3·48 †	28·0 ‡	8·05	0·75
CO_2Me	9·33	64·2	6·88	0·66
CO_2^-	21·2	170·5	8·04	0·66
CH_3	—	1·29	—	0·80
Cl	1·21	0·627	0·518	0·52
NH_2	—	0·230	—	0·61

* See p. 1476.
† Ratio of rate constants at 50° of *p*- and *o*-chloronitrobenzene.
‡ Ratio of rate constants at 50° of 1-chloro-2 : 4- and -2 : 6-dinitrobenzene.

are found experimentally. The effect is so marked that while *p*-CO_2^- is activating, *o*-CO_2^- is deactivating, particularly in the dinitro-series. The nature of the repulsive *ortho*-effect is clearly shown by the very high values of E. A more loosely bound transition state leads to high frequency factors also. In contrast, the *para*-compounds have quite low Arrhenius parameters.

The $+I(+M)$ methyl group is weakly deactivating. Its size is similar to that of the previous groups. The almost negligible *ortho*-effect is due to its lack of polar character.

The chloro- and amino-groups have opposing $-I$ and $+M$ effects. The former is activating and acts more strongly from the *ortho*-position : the latter is deactivating and acts more strongly from the *para*-position. The geometrical effects are also the smallest of the series. For both of these groups, therefore, *ortho*-acceleration may be considered probable, and further, this should be most marked for the amino-group since the *para*-deactivating $+M$ effect is so strong. Experimentally, *ortho*-acceleration is found for both groups and is stronger for the amino-group.

The activation by chloro and the deactivation by amino-groups due to the differing ratios of the I and M effects are, as expected, mainly associated with changes in E. However, the *o*-chloro-substituent in the dinitro-series has values of the Arrhenius parameters resembling those for the CO_2^- group. This is presumably associated with the negative field of the chlorine atom.

The following general conclusions may be drawn : (i) *ortho*-Effects are bigger in polar than non-polar compounds; (ii) they decrease in the order $-I$, $-T > -I$, $+M > +I(+M)$ groups; (iii) they tend to be accelerative for $-I$, $+M$ groups : this is associated with *para*-deactivation; (iv) they are generally bigger in the dinitro-series; *para*-effects vary much less, and are associated with a change in the extent of conjugation of the substituent group and the ring; (v) field effects are important; whereas (vi) geometrical effects are not.

EXPERIMENTAL

Kinetic investigations were carried out as in previous papers in this series (with one exception), end-points being obtained either electrometrically or with indicators. In the case of 4-chloro-3 : 5-dinitroaniline the runs were followed by electrometric estimation of chloride ion, since a side-reaction could not be satisfactorily allowed for by other means.

Preparations.—Those not recorded here are to be found in previous papers of the series (*locc. cit.*). M. p.s are corrected.

2-Chloro-5-nitrobenzoic acid, made from *o*-chlorobenzoic acid (Rupe, *Ber.*, 1897, **30**, 1099), had m. p. 165° (lit. 165°). Its methyl ester, made in 42% yield *via* the acid chloride, had m. p. 73° (lit. 73°). 2-Chloro-3 : 5-dinitrobenzoic acid, prepared from *o*-chlorobenzoic acid

(Ullmann, *Annalen*, 1909, **366**, 82), had m. p. 198° (lit. 199°), and its methyl ester (*idem*, *ibid.*) had m. p. 90° (lit. 88°). 2-Chloro-3 : 5-dinitrotoluene was made from *o*-cresol by dinitration (Gibson, *J.*, 1925, **127**, 45) followed by replacement of OH by Cl (Ullmann and Sane, *Ber.*, 1911, **44**, 3735); it had m. p. 63° (lit. 63—64°; 65°). 3 : 4-Dichloronitrobenzene, prepared from *o*-dichlorobenzene according to Hodgson and Kershaw (*J.*, 1929, 2922), had b. p. 254—256° (lit. 255—256°); n_D^{25} 1·5908.

1 : 2-Dichloro-4 : 6-dinitrobenzene was prepared by dinitration of *o*-chlorophenol followed by replacement of OH by Cl as above : m. p. 57° (lit. 56°).

2-Chloro-3 : 5-dinitroaniline, from the corresponding carboxylic acid (Blanksma and Verberg, *Rec. Trav. chim.*, 1934, **53**, 994), had m. p. 168° (lit. 168°).

4-Chloro-3-nitrobenzoic acid was prepared from *p*-chlorobenzoic acid as outlined by King and Murch (*J.*, 1925, **127**, 2646); the actual nitration was carried out at 65°, then for a few minutes at 90° until all material was in solution; The acid (90%) had m. p. 183° (lit. 182·5°). The methyl ester, prepared in 84% yield by standard procedures, had m. p. 83° (lit. 83°). Commercial 2 : 5-dichloro-1-nitrobenzene was purified to m. p. 54—55° (lit. 54·5°; 56°).

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301. *Synthetic Plant Hormones. Part I. Some Esters of Phosphoric Acid.*

By (MISS) M. H. MAGUIRE and G. SHAW.

Several chloroaryloxyethyl and chloroaryl hydrogen phosphates have been prepared in an attempt to elaborate a growth-controlling substance with selective activity against perennials with long tap-roots notably the skeleton weed (*Chondrilla juncea*).

THIS paper is concerned primarily with the synthesis of substances which may be effective in controlling the growth of plants with characteristically long tap roots, especially the skeleton weed (*Chondrilla juncea*), which cause heavy loss of wheat in New South Wales. From measurements of the hydrogen-ion concentration of skeleton-weed tissue to a depth of 33 inches and field work involving the mechanical destruction of the root at various levels, Greenham, Currie, and Allan (Austral. Counc. Sci. Ind. Res., Report No. 99, 1940) concluded that, to ensure effective control, a translocated poison is required which should penetrate the root to a depth of at least 4 feet and be soluble at pH 4·4—5·9 and toxic at pH 5·2—5·9.

Of the many chemicals investigated, the most effective—arsenic oxide, arsenious oxide, and sodium chlorate [Greenham *et al.*, *loc. cit.*; Cashmore and Carn, *J. Counc. Sci. Ind. Res.* (*Austral.*), 1940, **13**, 74; Greenham and Wilkinson, *ibid.*, 1942, **15**, 154; 1946, **19**, 341]—had an adverse effect on the wheat owing to partial sterilisation of the soil. Chloroaryloxyacetic acids (*idem*, *ibid.*, 1946, 341; Greenham, *Austral. J. Agr. Res.*, 1950, **1**, 148) gave no promise, probably because, having too great an initial toxicity, their movement in the plant was limited, the aerial parts alone being destroyed. We therefore attempted to elaborate molecules which would be (1) readily translocated by the plant (and consequently water-soluble) and (2) precursors of active plant-growth regulators, in particular, chloroaryloxyethyl and chlorophenyl hydrogen phosphates. Phosphates are known to move very readily in deep-rooted plants (Greenham, personal communication) and it was hoped that the chloroaryloxy-residues would provide a source of hormonal activity.

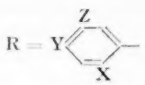
Plimmer and Burch (*J.*, 1929, 279) prepared alkyl hydrogen phosphates from an alcohol and excess of phosphorus oxychloride in chloroform, but the resultant mixture of mono- and di-esters obtained from 2 : 4-dichlorophenoxyethanol evinced little tendency

to hydrolyse in chloroform and thus could not be separated by means of water, and fractional distillation of the mixed acid chlorides led to extensive decomposition.

The required esters (I and II; X = Cl, Y = Z = H; Y = Cl, X = Z = H; X = Y = Cl, Z = H; and X = Y = Z = Cl) were obtained in excellent yield by boiling equimolecular amounts of the corresponding alcohol and phosphorus oxychloride in chloroform for 3 hours and hydrolysing the resultant mixed acid chlorides with a small amount of water. The dihydrogen phosphates (I) were then separated by dissolution in ice-cold ethanol. Under these conditions little or no neutral material (triesters, aryloxyethyl halides, etc.) could be detected.

$RO{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}PO(OH)_2$ (I)

$(RO{\cdot}CH_2{\cdot}CH_2{\cdot}O)_2PO{\cdot}OH$ (II)



$RO{\cdot}PO(OH)_2$ (III)

$(RO)_2{\cdot}PO{\cdot}OH$ (IV)

Numerous aryl hydrogen phosphates have been prepared (cf. Kosolapoff, "Organophosphorus Compounds," Wiley, New York; Jacobsen, *Ber.*, 1875, **8**, 1521; Rapp, *Annalen*, 1884, **224**, 156; Zetsche and Nachmann, *Helv. Chim. Acta*, 1926, **9**, 420; Rosenmund and Vogt, *Arch. Pharm.*, 1943, **281**, 317; Kekulé, *Ber.*, 1872, **5**, 876; 1873, **6**, 944), but usually in poor yield and of doubtful purity. However, good yields of the esters (III and IV; X = Cl, Y = Z = H; Y = Cl, X = Z = H; X = Y = Cl, Z = H; and X = Y = Z = Cl) were obtained by a modification of Rosenmund and Vogt's method (see Experimental section), which usually gave also some of the triester.

In preliminary tests for inhibition of germination the phosphate esters were compared with an equimolar amount of 2 : 4-dichlorophenoxyacetic acid (2 : 4-D) at a concentration equivalent to 5 lb. per acre, by Mr. C. G. Greenham of the Division of Plant Industry, C.S.I.R.O. The order of activity was 2 : 4-D > (I; X = Y = Cl, Z = H; or X = Z = H, Y = Cl) > (I or II; X = Y = Z = Cl) > (II; X = Y = Cl, Z = H) > (II; X = Z = H, Y = Cl) > (I or II; X = Cl, Y = Z = H), (III and IV; all variations). The final group of compounds was inactive whereas (I; X = Y = Cl, Z = H; and X = Z = H, Y = Cl) were only slightly less active than 2 : 4-D. The results suggest that possible precursors of a phenoxyacetic acid alone are active and that a 4-chloro-group is essential.

The esters were twice tested on mature skeleton weed with little or no effect; the plants used in these experiments, however, were unusually resistant to known poisons.

These results will be published in full elsewhere.

Experimental

The aryloxyethanols were prepared by Kirner's method (*J. Amer. Chem. Soc.*, 1926, **48**, 2748; cf. Powell, *J. Amer. Chem. Soc.*, 1923, **45**, 2709) from 2-chloroethanol (1 mole), the phenol (1·3 mole), and 2N-sodium hydroxide (1 l.) under reflux (30 min.). *2 : 4 : 5-Trichlorophenoxyethanol* separated from light petroleum as needles, m. p. 65—66° (Found: C, 39·8; H, 2·75. $C_8H_7O_2Cl_3$ requires C, 39·8; H, 2·9%).

2 : 4-Dichlorophenoxyethyl Hydrogen Phosphates (I and II; X = Y = Cl, Z = H).—2 : 4-Dichlorophenoxyethanol (60 g.) in chloroform (300 ml.) was added gradually with stirring to phosphorus oxychloride (60 g.) in chloroform (200 ml.). The solution was boiled under reflux for 3 hours, then evaporated *in vacuo* to an oily residue which was heated on the steam-bath with water (20 ml.) for 3 hours with stirring. The crystalline mass which separated on cooling was stirred with ice-cold ethanol, and the solid filtered off; *di-(2 : 4-dichlorophenoxyethyl) hydrogen phosphate* crystallised from benzene as needles (35 g.), m. p. 141° (Found: C, 40·9; H, 3·5%; equiv., 476. $C_{16}H_{15}O_6Cl_4P$ requires C, 40·35; H, 3·2%; equiv., 476). Attempted hydrolysis of the diester with aqueous sodium hydroxide gave the *sodium* salt only, needles (from water), m. p. 300° (Found: C, 38·4; H, 2·85. $C_{16}H_{14}O_6Cl_4PNa$ requires C, 38·6; H, 2·85%). Evaporation of the above alcoholic extract *in vacuo* gave an oil which crystallised. *2 : 4-Dichlorophenoxyethyl dihydrogen phosphate* (30 g.) separated from chloroform as needles, m. p. 111—112°, soluble in water and ethanol (Found: C, 33·45; H, 3·15%; equiv., 143. $C_8H_9O_5Cl_2P$ requires C, 33·45; H, 3·15%; equiv., 143·5). Distillation of the mixture of acid chlorides *in vacuo* resulted in extensive decomposition and formation of a purple gum.

Similar experiments led to: *bis*-o-*chlorophenoxyethyl hydrogen phosphate* (56·5 g. from 80 g. of the alcohol), needles (from toluene), m. p. 135—136° (Found: C, 47·1; H, 4·2%; equiv., 405. $C_{16}H_{17}O_6Cl_2P$ requires C, 47·2; H, 4·2%; equiv., 407), and o-*chlorophenoxyethyl dihydrogen phosphate* (30 g.), plates (from chloroform), m. p. 143—144° (Found: C, 37·75; H, 3·8%; equiv., 126. $C_8H_{10}O_5ClP$ requires C, 38·05; H, 4·0%; equiv., 126); *bis*-p-*chlorophenoxyethyl hydrogen phosphate* (30 g. from 80 g.), needles (from ethanol–water), m. p. 164° (Found: C, 46·95; H, 4·5%; equiv., 405), and p-*chlorophenoxyethyl dihydrogen phosphate* (25 g.), plates (from chloroform), m. p. 127° (Found: C, 37·8; H, 4·0%; equiv., 126); and *di*-(2 : 4 : 5-*trichlorophenoxyethyl*) *hydrogen phosphate* (21 g. from 83 g.), needles (from ethanol–water), m. p. 172° (Found: C, 35·2; H, 2·4%; equiv., 547. $C_{16}H_{13}O_6Cl_6P$ requires C, 35·25; H, 2·4%; equiv., 545), and 2 : 4 : 5-*trichlorophenoxyethyl dihydrogen phosphate* (27 g.), needles (from acetone–chloroform), m. p. 139—140° (Found: C, 30·05; H, 2·65%; equiv., 159·5. $C_8H_8O_5Cl_3P$ requires C, 30·0; H, 2·5%; equiv., 161).

2 : 4-*Dichlorophenyl Hydrogen Phosphates* (III and IV; X = Y = Cl, Z = H).—2 : 4-Dichlorophenol (65 g.), phosphorus oxychloride (69 g.), and magnesium turnings (0·1 g.) were kept at 130—140° for 3 hours, hydrogen chloride being steadily evolved. Distillation *in vacuo* (air-stream dried with P_2O_5) gave 2 : 4-*dichlorophenylphosphorodichloridate* (51 g.) as a dense, colourless, fuming liquid, b. p. 115°/1·5 mm. (Found: C, 25·9; H, 1·25. $C_6H_3O_2Cl_4P$ requires C, 25·75; H, 1·1%). This (42·8 g.) was slowly added to warm water (100 ml.) with stirring; when cooled, the solution deposited 2 : 4-*dichlorophenyl dihydrogen phosphate* (32 g.) which separated from toluene as needles, m. p. 65—66° (Found: C, 29·7; H, 2·25%; equiv., 121·5. $C_6H_5O_4Cl_2P$ requires C, 29·65; H, 2·05%; equiv., 121·5). A further 5 g. of the acid were extracted from the aqueous solution with ether. The residue (45 g.) from the distillation was largely di-(2 : 4-dichlorophenyl) phosphorochloridate and was hydrolysed on the water-bath with 2N-sodium hydroxide (500 ml.). When cooled, the solution deposited a small amount (1 g.) of *tri*-(2 : 4-*dichlorophenyl*) *phosphate* which crystallised from light petroleum as needles, m. p. 95° (Found: C, 40·7; H, 1·85. $C_{18}H_9Cl_6P$ requires C, 40·55; H, 1·7%). The alkaline filtrate was strongly acidified with hydrochloric acid and extracted with ether (3 × 100 ml.); evaporation of the extract left a crystalline solid (45 g.) which had a strong phenolic odour. The solid was triturated with 10% potassium carbonate solution and the salt which separated was washed with dry ether (it is soluble in moist ether) and ground with a slight excess of 5N-hydrochloric acid, giving *di*-(2 : 4-*dichlorophenyl*) *hydrogen phosphate* (20 g.) (from chloroform–light petroleum), m. p. 131° (Found: C, 37·0; H, 2·05%; equiv., 385. $C_{12}H_7O_4Cl_4P$ requires C, 37·15; H, 1·8%; equiv., 388).

Similar experiments gave 2 : 4 : 5-*trichlorophenyl phosphorodichloridate* (45·6 g. from 79 g. of phenol), b. p. 115—119°/0·5 mm. (Found: C, 23·7; H, 0·7. $C_6H_2O_2Cl_5P$ requires C, 22·9; H, 0·9%; the poor analysis may be due to slight hydrolysis), 2 : 4 : 5-*trichlorophenyl dihydrogen phosphate* (26 g. from 38·6 g. of dichloride), needles (from chloroform–light petroleum), m. p. 179° (Found: C, 25·8; H, 1·6%; equiv., 138·5. $C_6H_4O_4Cl_3P$ requires C, 25·95; H, 1·45%; equiv., 138·8), *tri*-(2 : 4 : 5-*trichlorophenyl*) *phosphate* (3·1 g.), needles (from chloroform–light petroleum), m. p. 161—162° (Found: C, 34·0; H, 1·15. $C_{18}H_6O_4Cl_9P$ requires C, 34·0; H, 0·95%), and *di*-(2 : 4 : 5-*trichlorophenyl*) *hydrogen phosphate monohydrate* (20·5 g.), needles (from chloroform–light petroleum), m. p. 152—153° (Found: C, 30·6; H, 1·5%; equiv., 474. $C_{12}H_5O_4Cl_6P,H_2O$ requires C, 30·4; H, 1·5%; equiv., 475); *o*-chlorophenyl phosphorodichloridate (30·7 g. from 51·4 g. of phenol), b. p. 85°/0·6 mm. (Anschutz, *Annalen*, 1918, **415**, 64, gives b. p. 135—137°/12 mm.), n-*amylammonium* o-*chlorophenyl phosphate*, plates (from methanol–ether), m. p. 179—180° (Found: C, 50·25; H, 8·3; N, 7·15. $C_6H_6O_4ClP,2C_5H_{13}N$ requires C, 50·2; H, 8·35; N, 7·3%), di-*o*-chlorophenyl hydrogen phosphate (23 g.), plates (from chloroform–light petroleum), m. p. 120° (Found: C, 44·55; H, 2·9%; equiv., 316. Calc. for $C_{12}H_9O_4Cl_2P$: C, 45·15; H, 2·85%; equiv., 319) (Brusch and Kechin, *Rec. Fac. sci. Univ. Istanbul*, 1942, 7*a*, 182, give m. p. 121·5°); *p*-chlorophenyl phosphorodichloridate (64 g. from 51·4 g. of phenol), b. p. 91—94°/0·8 mm. (Rosenmund and Vogt, *loc. cit.*, record b. p. 95—115°/0·1 mm., and Zetsche and Nachmann, *loc. cit.*, b. p. 142°/11 mm.), p-*chlorophenyl dihydrogen phosphate hemihydrate* (40 g.), needles (from benzene–chloroform), m. p. 123—124° (Found: C, 33·3; H, 3·15%; equiv., 108·4. $C_6H_6O_4ClP,\frac{1}{2}H_2O$ requires C, 33·1; H, 3·25%; equiv., 108·8), and di-*p*-chlorophenyl hydrogen phosphate (17 g.), plates (from chloroform–light petroleum), m. p. 131—132° (Found: C, 44·95; H, 2·8%; equiv., 319·5) (Zetsche and Nachmann, *loc. cit.*, give m. p. 133—135°).

The approximate dissociation constants of the acids (I and III) at M/50-concentration and of (IV) at M/500, in water at 23—25°, were determined from the titration curves (Cambridge

pH meter) and are tabulated below; the acids (II) were too insoluble in water for accurate measurement.

Compound	10^3K_{a1}	10^7K_{a2}	Compound	10^3K_{a1}	10^7K_{a2}
(I; X = Cl, Y = Z = H)	9·32	2·82	(IV; X = Cl, Y = Z = H) ...	0·226	—
(I; Y = Cl, X = Z = H)	9·41	3·16	(IV; Y = Cl, X = Z = H) ...	0·130	—
(I; X = Y = Cl, Z = H)	8·94	2·82	(IV; X = Y = Cl, Z = H) ...	0·226	—
(I; X = Y = Z = Cl)	9·21	2·82	(IV; X = Y = Z = Cl)	0·256	—
(III; Y = Cl, X = Z = H) ...	9·49	15·9			
(III; X = Y = Cl, Z = H).....	9·32	23·5			
(III; X = Y = Z = Cl)	9·32	50·1			

The authors thank Mr. C. G. Greenham at whose request this work was undertaken, the Commonwealth Scientific and Industrial Research Organisation for a maintenance grant (to M. H. M.), Timbrol Ltd. for gifts of chemicals, and Dr. E. Challen for the semi-micro analyses.

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302. *Cyclic Meso-ionic Compounds. Part V.* Further Studies on the Stereochemistry of the Sydnones, with a Description of a Heterodyne Capacitance Meter for Dielectric-constant Measurements in the Range 2—3.*

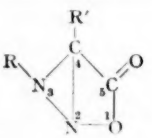
By R. A. W. HILL and L. E. SUTTON.

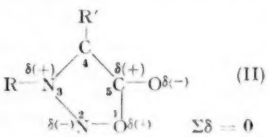
Electric dipole-moment measurements on 4-chloro-3-*p*-chlorophenylsydnone, on 3 : 4-diphenylsydnone and its *p*-chloro-derivatives (two mono- and one di-substituted), and on the corresponding *p*-tolyl compounds, provide further evidence (cf. Part II, Hill and Sutton, *J.*, 1949, 746) that, in the sydnones, the radial bond from nitrogen lies in the plane of the ring, or very near thereto. Also, closer limits have been found for the angle between this valency and the one which radiates from the neighbouring carbon atom (76—83°), which make it probable that the latter bond also lies in, or nearly in, the plane of the ring.

Both of these stereochemical conclusions support the monocyclic structure with non-localised π-bonds, the so-called meso-ionic structure, which was recently proposed.

We now describe the capacitance meter used for the measurements reported in this and in related papers published since 1947. It is of the heterodyne type; and it gives adequate sensitivity (±0·0001), combined with ease of operation, for dielectric constants in the range 2—3.

ELECTRIC dipole moments have been used by two groups of workers to investigate the structure of the sydnones (Earl, Leake, and Le Fèvre, *Nature*, 1947, **160**, 366; *J.*, 1948, 2269; Baker, Ollis, Poole, Barltrop, Hill, and Sutton, *Nature*, 1947, **160**, 366; Hill and Sutton, *J.*, 1949, **746**; *J. Chim. physique*, 1949, **46**, 244). The principal aim has been to discover whether the dicyclic structure (I) or the recently proposed monocyclic structure (II) is the more correct. The latter can be formulated either as a hybrid of a number of

(I) 



(II)

zwitterionic structures or, following the molecular-orbital procedure, as a structure with partial formal charges (see Baker, Ollis, and Poole, *J.*, 1949, 307; Hill and Sutton, *loc. cit.*); this is represented qualitatively in formula (II).

Two tests have been applied. The first is based on the absolute magnitude of the actual

* Part IV, *J.*, 1951, 289.

moment, which has already been shown to be in substantially better agreement with that expected from (II) than with that from (I). By using new parameters in an empirically corrected molecular-orbital treatment, a revised value has been calculated for the π-electron moment, *viz.*, 5·6 D (Orgel, Cottrell, Dick, and Sutton, *Trans. Faraday Soc.*, 1951, **47**, 113), which agrees quite well with the observed value of 4·6—5·4 D previously reported (Hill and Sutton, *loc. cit.*). In the present paper, an attempt has been made to narrow the limits of the observed value.

The second test is based on the stereochemistry of the system. Were formula (I) correct, the bonds R–$N_{(3)}$ and R′–$C_{(4)}$ should not be coplanar with the ring but might be up to 55° out of its plane; whereas if formula (II) were correct, the σ-bonds round $C_{(4)}$ and $N_{(3)}$ (which latter has a large positive formal charge) would probably arise from sp^2 hybridisation and be approximately planar, so that the two bonds mentioned would be coplanar with the ring and with each other. This test has not previously given a conclusive answer, although in 3-phenylsydnones the bond Ph–$N_{(3)}$ has been shown to lie within 20° of the plane of the ring. Further measurements are now reported which bear on this. They also relate to the angle between the valencies radiating from atoms $N_{(3)}$ and $C_{(4)}$, and to the angle which μ_m makes with the ring system.

Experimental

Preparation and Purification of Materials.—Benzene. Analytical-grade material was purified as described in Part II (Hill and Sutton, *loc. cit.*).

Sydnones. The sydnones were provided by Professor Wilson Baker and Drs. W. D. Ollis and V. D. Poole (Bristol). Their preparations and characteristics have been reported (*J.*, 1949, 307; 1950, 1542)

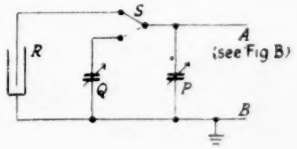
Physical Measurements.—Dielectric constants. A heterodyne-beat capacitance meter was used. This instrument, having proved satisfactory during five years of regular use, is now described in greater detail. It was designed for rapid, routine measurements in the range 2—3.

The principles of measurement are the same as those used earlier (see Sutton, *Proc. Roy. Soc.*, 1931, *A*, **133**, 668), *i.e.*, the dielectric constants of air (e_1) and of benzene (e_2) are assumed known, so if e_3 is the value for a solution, and c_1, c_2, and c_3 are the corresponding capacities, then

$$e_3 = (e_2 - e_1)(c_3 - c_1)/(c_2 - c_1) + e_1$$

provided that, in the liquid cell, few lines of force pass through more than one medium and that lead capacitances stay constant. The capacitances need be known only in units of an arbitrary linear scale.

Fig. A.



The circuit of the measuring system is shown in Fig. A,* P is an uncalibrated variable capacitor and S is a change-over switch by means of which the calibrated capacitor Q and the cell R may be interchanged; R is connected, and P is adjusted until the difference of frequency from an arbitrary reference frequency, *i.e.*, $f_1 - f_0$, is simply related to a fixed audio-frequency f_2; then Q is connected and adjusted to give the same result. The process is repeated to compare Q and R accurately, the precision being limited only by the reproducibility of capacitances within the switch S and those for the step units in Q (see later), and by uncontrolled disturbances occurring during the time required to operate S. These factors are made smaller than corresponds to the required precision ($\pm 10^{-4}$), with the result that very rapid and reliable measurements are possible; moreover, changes of dielectric constant with time are easily followed.

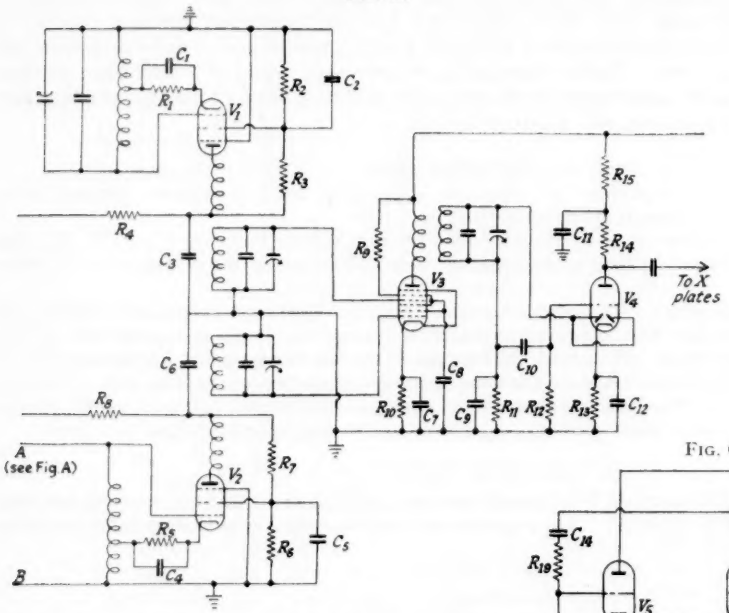
P consists of two capacitors, allowing coarse and fine adjustment; Q consists of the cylindrical capacitor already specified (Sutton, *loc. cit.*) and a set of six silica-insulated capacitors

* Figures in this paper are denoted by letters in order to distinguish them from those of Part II, to which frequent reference is made and which are distinguished numerically as usual.

which can be switched in by keys; R is similar to the cell described by H. O. Jenkins and Sutton (*J.*, 1935, 609) save that the insulated electrode is hollow, and that inside it is a concentric, earthed cylinder forming part of the base assembly; so the electrical capacity is increased to about 50 pF, and the fluid capacity reduced to about 40 ml.* The switch S is a rotary one which gives small and reproducible capacitances between contacts. It consists of a rectangular duralumin plate (2″ × 3″) having a spindle through the middle, and at each corner a polystyrene pillar carrying a gold–platinum alloy contact. A polystyrene rod attached to the spindle is slotted axially and across a diameter to carry a silver-plated phosphor-bronze strip which rotates with it and connects together with a wiping action either pair of the diagonally-placed contacts. To give the required operation, two adjacent contacts are connected together.

The apparatus is in three rack-mounted units. The main unit (I), which is essentially a

FIG. B.

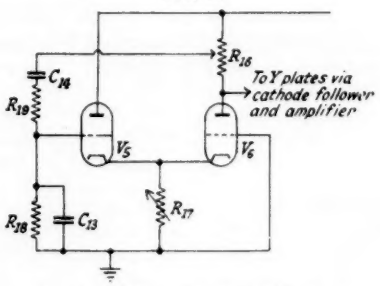


R_1, R_5 = 5 kΩ; R_2, R_8 = 30 kΩ; R_3, R_7, R_{14} = 50 kΩ; R_4, R_6 = 20 kΩ; R_9 = 60 kΩ; R_{10} = 300 Ω; R_{11} = 500 kΩ; R_{12} = 1 meg. Ω; R_{13} = 1 kΩ; R_{15} = 15 kΩ.

C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8 = 0·1 mF.; C_9 = 0·0002 mF.; C_{10} = 0·02 mF.; C_{11} = 8 mF.; C_{12} = 50 mF.

V_1, V_2 = EF 36; V_3 = EK 32; V_4 = EBC 33.

FIG. C.



R_{16} = 100 kΩ; R_{17} = 5 kΩ; R_{18}, R_{19} = 200 kΩ.

C_{13}, C_{14} = 0·001 mF.

V_5, V_6 = H 63.

beat-frequency generator, contains the measuring system and the two radio-frequency oscillators together with subsidiary circuits for mixing, de-modulation, and beat-frequency amplification. The output (frequency $f_1 - f_0$) has an amplitude determined largely by the selectivity of the mixing circuits which are peaked at f_0. This makes the initial rough tuning very simple. f_0 is approx. 600 kc./sec., which is high enough to give adequate sensitivity but low enough to ensure that the total inductance needed to resonate with the capacitances to be measured is large compared with lead inductances.

The second unit (II) contains an audio-frequency oscillator (f_2 is approx. 1000 cycles/sec.) and a small cathode-ray tube the Y plates of which carry f_2 and the X plates $f_1 - f_0$. The

* A miniature glass cell, used subsequently, is described by Everard and Sutton (*J.*, 1951, 16).

necessary relation between these two frequencies is obtained by tuning to a Lissajous figure; the " figure of eight " corresponding to $\overline{f_1 - f_0} = f_2/2$ is convenient and does not give any loss of sensitivity due to the oscillators " pulling."

Details of the main unit (I) are shown in Fig. B. The oscillators are electron-coupled and the inductive coupling in the plate circuits is made as loose as is compatible with a usable output. Frequency stability is thus improved, and " pulling " is made small. Great care was taken to construct the unit rigidly in order to keep stray capacitances constant. The coils are mounted inside strong brass screening cans in such a way that there would be no relative movement should the main chassis become twisted. The circuits and layouts of the oscillators are as nearly identical as possible, so that disturbances common to both, particularly supply-voltage fluctuations, will have an equal effect on f_0 and f_1.

The audio-frequency oscillator, the circuit of which is shown in Fig. C, is governed by a Wien bridge. The output is taken through a cathode follower (valve type 6C5) and an amplifier (valve type 6C5)

The power supplies (unit III) are conventional except that there are two high-tension supplies: a regulated supply for the oscillators and cathode follower and an unregulated supply for the other valves. The heaters of the oscillator and cathode follower valves are supplied from a voltage-regulating transformer. The supply for the cathode-ray tube is in unit II.

The linearity of the standard capacitor Q may conveniently be checked by using two Lissajous figures to define a small capacity increment (cf. Groves, *J.*, **1939**, 1144); though, as a further check, a calibration was made by the usual method of repeatedly connecting and disconnecting a small fixed capacitance, and was found to agree within the required limits.

The lead from unit I to the cell R, which is immersed in a thermostat (usually at 25°), is taken through a brass tube $\frac{3}{4}$" in diameter in which it is fixed and insulated with polystyrene discs. Ordinary concentric cable was insufficiently stable.

Specific Volumes.—A pyknometer was used as described in Part II (*loc. cit.*).

Refractive Indices.—Measurements were made with a Jamin interferometer as described in Part II, but these results have since been discarded as unreliable because of a possible dispersion-effect error (Everard, Hill, and Sutton, *Trans. Faraday Soc.*, 1950, **46**, 417). Instead, electron polarisations calculated from Earl, Leake, and Le Fèvre's observed value for *N*-phenylsydnone (*loc. cit.*) have been used. The largest discrepancy between the old and the new values is 8·6 c.c., corresponding to a change in moment of 0·03 D. Fortunately, all the moments reported in Part II are negligibly altered (by 0·01 D or less) by the recalculation.

Results.—The observed and derived numerical values are given in Table 1, the symbols having the same meaning as in Part II. The procedure for calculating electric dipole moments is also the same (cf. Everard, Hill, and Sutton, *loc. cit.*).

TABLE 1.

$w \cdot 10^6$	ϵ	v	$w \cdot 10^6$	ϵ	v	$w \cdot 10^6$	ϵ	v
3 : 4-*Diphenylsydnone*			4-*Phenyl*-3-p-*tolylsydnone*			3 : 4-*Di*-p-*chlorophenylsydnone*		
1994	2·3130	1·1441	1153	2·2974	1·1451	334	2·2751	—
3441	2·3415	1·1435	2589	2·3281	1·1444	959	2·2800	—
4895	2·3703	1·1429	2716	2·3306	1·1443	1870	2·2871	1·1445
7300	2·4183	1·1420	4891	2·3765	1·1436	2965	2·2958	1·1438
						3960	2·3038	—
3-*Phenyl*-4-p-*tolylsydnone*			4-p-*Chlorophenyl*-3-*phenylsydnone*			4975	2·3121	1·1426
1482	2·3018	1·1450	(175)	(2·2764) *	—	7512	(2·3310) †	1·1414
2997	2·3316	1·1446	557	2·2810	—			
3836	2·3482	1·1443	1096	2·2891	—	4-*Chloro*-3-p-*chlorophenylsydnone*		
4631	2·3638	1·1441	2123	2·3041	1·1443	1950	2·2940	1·1446
			4796	2·3445	1·1429	3988	2·3175	1·1433
3 : 4-*Di*-p-*tolylsydnone*			6132	2·3648	1·1421	6383	2·3455	1·1422
866	2·2907	—	8120	2·3954	1·1412	7876	2·3621	1·1413
1562	2·3055	1·1450						
2027	2·3162	—	3-p-*Chlorophenyl*-4-*phenylsydnone*			4-*Nitro*-3-*phenylsydnone* ‡		
2893	2·3345	1·1445	3069	2·3066	1·1435	313	2·2781	—
3623	2·3495	1·1445	4730	2·3250	1·1427	720	2·2865	1·1446
5006	2·3787	1·1437	7037	2·3501	1·1418	1074	2·2938	1·1444
			9117	2·3726	1·1408	1465	2·3015	1·1443

* This point was rejected because, although it is only slightly off the straight line, the least-square procedure overemphasises points at either end of the range of readings.

† This point was rejected because there appears to be curvature in the graph starting some way below this point. The other points are, however, on a good straight line.

‡ Measurements by Mr. P. G. Edgerley.

TABLE 2.

Compound	a	α	b	β	$_TP$	$_EP$	μ, D
3 : 4-Diphenylsydnone	2·2729	19·91	1·1448	−0·40	945·3	69·7	6·55
3-Phenyl-4-*p*-tolylsydnone	2·2728	19·63	1·1454	−0·29	996·2	74·5	6·72
4-Phenyl-3-*p*-tolylsydnone	2·2729	21·22	1·1455	−0·39	1063·9	74·5	6·96
3 : 4-Di-*p*-tolylsydnone	2·2727	21·21	1·1455	−0·34	1125·7	79·4	7·15
4-*p*-Chlorophenyl-3-phenylsydnone	2·2725	15·09	1·1454	−0·53	824·1	74·6	6·06
3-*p*-Chlorophenyl-4-phenylsydnone	2·2729	10·96	1·1448	−0·44	619·5	74·6	5·16
3 : 4-Di-*p*-chlorophenylsydnone ...	2·2724	7·93	1·1454	−0·54	513·4	79·5	4·61
4-Chloro-3-*p*-chlorophenylsydnone	2·2717	11·51	1·1456	−0·55	542·2	55·0	4·88
4-Nitro-3-phenylsydnone	2·2711	20·34	1·1448	−0·50	832·4	52·6	6·18

The errors in the dipole-moment values are estimated to be ±0·02 D.

DISCUSSION

In Part II (*J.*, 1949, 746), some progress towards complete elucidation of the molecular geometry was made by solving certain of the relevant vector triangles. Thus, from the electric dipole moments of 3-phenylsydnone itself, its 3-*p*-chlorophenyl and its 4-chloro- or -bromo-derivatives, and assumed values for the grouping Ph–$N_{(3)}$ and for the substitution moment of chlorine [taken as μ(PhCl)], the triangles *ABC*, *ABC'*, and *ADB* were solved as shown by Figs. 1, 2, and 3 of that paper; * *i.e.*, the relative directions of the moments of (*a*) 3-phenylsydnone (*AB* in Fig. 1), chlorobenzene (*BC*), and 3-*p*-chlorophenylsydnone (*AC*), (*b*) 3-phenylsydnone (*AB* in Fig. 2), the Ph–$N_{(3)}$ bond (*BC'*), and the sydnone ring itself (*AC'*, or μ_S), (*c*) 3-phenylsydnone (*AB* in Fig. 3), the halogenobenzene (*DA*), and the 4-halogeno-3-phenylsydnone (*BD*), could be ascribed in these three sets considered separately as the vector triangles *ABC*, *ABC'*, and *ABD*, respectively. The relation of the planes of the triangles *ABC* and *ADB* was, however, indeterminate; so it was possible only to say that the angle between the bonds Ph–$N_{(3)}$ and Hal–$C_{(4)}$ lay between the rather wide limits of 65° and 97° as shown by Figs. 4 and 5.

The plane of the triangle *ABC'* relative to *ADB* was likewise indeterminate, so the only statement which could be made about the direction of the Ph–$N_{(3)}$ vector (*BC'*) was that it is at about 20° (±5°) to *AC'*. *AC'* was taken to be the moment of the sydnone ring itself; whence it was concluded that Ph–$N_{(3)}$ could actually be in the ring plane or up to 20° out of it (Fig. 6). This is not strictly true, because *AC'* (μ_S) is really the ring moment proper plus the vector due to the R'–$C_{(4)}$ moment which may not lie in the ring plane; so we do not necessarily know the orientation of Ph–$N_{(3)}$ relative to the atoms of the ring until and unless the orientation of the R'–$C_{(4)}$ bond thereto can be determined; though if the moment of R'–$C_{(4)}$ (which is either H–C or Ph–C) is small, this point is not important.

The problem, regarded as one in simple vector analysis, requires the evaluation of the three angles between three moment vectors which are not necessarily coplanar. Supposing, as was done in the previous paper, that there are no interaction moments to be evaluated in addition (see, *e.g.*, Sutton and Hampson, *Trans. Faraday Soc.*, 1935, **31**, 945), this requires three observations. These may be provided by measuring the three independent changes of moment which occur between the parent compound, its two isomeric monosubstituted derivatives, and its disubstituted derivative. The vector problem might therefore just be soluble; but even then the orientation of the ring plane cannot be related to the directions of the dipoles without making assumptions or adducing information external to the moment measurements. Therefore there is no prospect of a general, complete, and rigorous solution of the problem from dipole measurements alone; but at least it is an interesting exercise to see how far the enquiry can usefully be pushed.

The measurement of the moment of 4-chloro-3-*p*-chlorophenylsydnone permits the solution of a further triangle *ACE* (cf. Figs. D and E, where *AC* is again the moment of 3-*p*-chlorophenylsydnone, *CE* that of the $C_{(4)}$–Cl bond, and *AE* that of the 4-chloro-3-*p*-chlorophenyl-compound). Furthermore, because both *DA* in Figs. 3, 4, and 5 and *CE* in Fig. D or E refer to the same bond ($C_{(4)}$–Hal),† it would appear possible to apply a test of

* Cf. footnote, p. 1483.

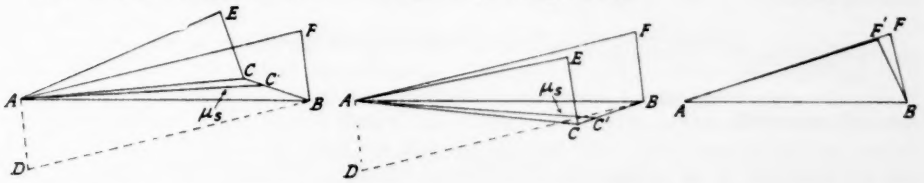
† The actual values in Figs. 3, 4, and 5 of Part II are for the bromo-compound. For the chloro-compound $\angle DAB$ is 83°.

consistency by adding triangle *ACE* to Figs. 4 and 5 and seeing which of these makes *DA* and *CE* more nearly parallel, as they must be from their physical significance.

For a reason which will appear later, in Figs. D and E , which incorporate Figs. 4 and 5 and show these relations, the vector triangle *ABF* is shown as an alternative, equivalent representation of the triangle *ABD* (broken line) which was used in the previous paper. From these figures it may be seen that consistency is obtained only if triangle *ACE* is joined, in the manner shown, to the 0° configuration, *i.e.*, to Fig. 5, when *BF* (≡ *DA*) and *CE* prove to be parallel to within the limits of experimental error (see Fig. E), the angle between them being only 2·5°. With the 180° disposition of Fig. D, *DA* (≡ *BF*) and *CE* are 15° out of parallel.

It therefore appears possible to obtain an essentially satisfactory solution of all the vector relations with the configuration shown in Fig. E. This requires that *AC*, *BC*, and *BF* (≡ *DA*, or = *CE*) be coplanar. It therefore requires also that *BC'*, *BF*, and *AC'* be coplanar, *i.e.*, that the Ph–$N_{(3)}$ bond, the substitution moment along the $C_{(4)}$–Hal bond, and all the rest of the 3-phenylsydnone moment beyond that due to the Ph–$N_{(3)}$ bond, shall be coplanar. Much the most probable explanation of this vectorial condition is that the ring is planar and that the Ph–$N_{(3)}$ and the $C_{(4)}$–Hal bonds lie in this plane. These conclusions would obviously provide strong support for the hybrid monocyclic structure (II).

FIG. D. (180° configuration.) FIG. E. (0° configuration.) FIG. F.



The series of compounds produced by *p*-chloro-substitution in 3 : 4-diphenylsydnone can be used in exactly the same way : *AB* now corresponds to the moment of 3 : 4-diphenylsydnone, *BC*, *BF*, and *CE* to that of chlorobenzene, *AC* to that of 3-*p*-chlorophenyl-4-phenylsydnone, *AF* (≡ *DB*) to 4-*p*-chlorophenyl-3-phenylsydnone, and *AE* to 3 : 4-di-*p*-chlorophenylsydnone. Essentially the same result is obtained in that the 0° configuration for triangles *ABC* and *ADB* is required for *BF* (≡ *DA*) and *CE* to be nearly parallel, the angle between them then being 2·5°.

From the similar series produced by *p*-methyl substitution a rather different result is obtained, because the moment of 4-phenyl-3-*p*-tolylsydnone (6·96) is equal within experimental error to the sum of the moments of the parent compound 3 : 4-diphenylsydnone (6·55) and of toluene (0·35—0·40); so there is no ambiguity of orientation of vector triangles to be resolved, and the whole sydnone moment is found to be collinear with the axis of the 3-phenyl group, a relation which must be accidental. This result indicates very directly that the Ph–$N_{(3)}$ bond is coplanar with the sydnone ring; but because the substitution moment due to the methyl group is so small, the value of this indication is uncertain.

From all three series it is possible to derive values for the angle between the Ph–$N_{(3)}$ and X–$C_{(4)}$ valencies : in the first two, because the vectors *DA* and *CE* are parallel within 3° in the 0° configurations for each, the valency angles from these should be definite within this limit; but from the corresponding 180° configurations they are indefinite within 11—15°. The third series gives a single definite value. These are all given in Table 3.

It is also possible to estimate the magnitude and direction of the π-electron moment. This may be done if it be assumed that, though the sydnone ring remains a regular pentagon, the valencies radiating from it may be distorted from the regular pentagonal axes, any such distortion of the Ph–$N_{(3)}$ and X–$C_{(4)}$ bonds being symmetrical; so that the bisector of the angle between these two bonds is at 54° to the $N_{(2)}$–$O_{(1)}$ bond in the ring. Having thus assumed a relation between two moment vectors (*BC* and *BF* or *CE*) and the ring

skeleton, the direction of μ_S (AC') is fixed relative to it. Since a rough evaluation of the σ-bond moment for the skelton, relative to $N_{(2)}$–$O_{(1)}$, has been made in Part II, the magnitude being 1·3 D and the direction −68°, this vector may then be subtracted from μ_S to give the magnitude and direction of the π-electron moment. The results of such calculations also are tabulated below.

From this Table it will be remarked that for the first two series the 0° configurations, which were judged the better ones by the consistency test, give large though not impossible values for the intervalency angle between the Ph–$N_{(3)}$ and the Hal–$C_{(4)}$ or Ph–$C_{(4)}$ bonds; but they also give values for μ_π which, while agreeing fairly well in magnitude, disagree badly in direction with those calculated by a molecular-orbital procedure. The latter

TABLE 3.

Configuration	Magnitude of μ_π, D	Direction of μ_π relative to $N_{(2)}$–$O_{(1)}$	Intervalency angle
	3-Phenyl-4-H series, chlorine substitution (first series)		
0°	4·65	−12°	98·5°
180°	5·0—5·15	+5·5°—13°	55°—67·5°
	3 : 4-Diphenyl series, chlorine substitution (second series)		
0°	4·5	−27°	89·5°
180°	4·9—5·0	+1·5°—7·5°	31°—42°
	3 : 4-Diphenyl series, methyl substitution (third series)		
Coincident	4·65	−9°	65°
	3-Phenyl-4-H series, chlorine substitution (modified first series)		
Assumed coincident	4·85	−2°	76°—83·5°
	3 : 4-Diphenyl series, chlorine substitution (modified second series)		
Assumed coincident	4·7	−10·5°	61°—65°
	Computed values *		
	5·6	+6°	72° †

* From Orgel, Cottrell, Dick, and Sutton (*loc. cit.*). *Note.*—In that paper angles measured clockwise were denoted as positive; in the present paper the more usual convention is observed.

† For a regular pentagonal ring. Enlargement might be expected.

The value of μ(PhCl) used above is 1·55 D, being derived by recalculating the data reported by Davis, Bridge, and Svirbely (*J. Amer. Chem. Soc.*, **1943**, **65**, 857). Everard and Sutton (*J.*, 1951, 2807) use 1·60, derived from Le Fèvre and Le Fèvre's data (*J.*, 1936, 1130). Having regard to the nature of the assumptions made, this difference is trivial for the above calculations.

direction is in qualitative agreement with the expectations from the "resonance" interpretation of the problem; so the discrepancy is disturbing. The 180° configurations give intervalency angles which are smaller than the minimum value to be expected (72°); but they give reasonably good agreement between the observed and the calculated π-electron moment vectors. The third series gives only one set of results, showing a somewhat small intervalency angle and only fair agreement between observed and calculated π-electron moment vectors.

These observations suggest that there are interaction moments, which cannot be ignored, between the chlorine atom substituted in the 3-phenyl group and the sydnone ring *para* to it. If these are such as to reduce numerically the apparent substitution moments by chlorine, the difference between the results for the 0° and 180° configurations in each series is less, and will vanish if the substitution moment becomes equal to the numerical difference between the moments of the parent compound and the 3-*p*-chloro-derivative, *i.e.*, equal to 1·47 and 1·40 respectively for the first and second series, corresponding to interaction moments of 0·08 and 0·15 D, respectively. Then, as indicated already in the third series, the Ph–$N_{(3)}$ bond would be collinear with the total sydnone moment. The results in this limit, for μ_π and the intervalency angles are also tabulated, being designated as from the modified first and second series of measurements.

Values from the second modified series and the third series agree quite well, though both give a value for the intervalency angle which is less than the likely minimum, and neither gives very good agreement with the calculated magnitude or direction of the

π-electron moment. The modified first series gives a quite probable mean value (80°) for the intervalency angle, and quite good values for the magnitude and direction of the π-electron moment. Thus, both sets of derivatives from 3 : 4-diphenylsydnone agree in giving rather anomalous results, whereas those from 3-phenylsydnone give reasonable ones. This may indicate yet another kind of interaction moment.

Because of these complications it is now clear that there is no hope of a rigorous solution, even of the vector problem, unless the interactions can be evaluated independently. This might be possible if they were due only to electrostatic induction; so it has been attempted by the standard procedure (see, *e.g.*, Hampson and Weissberger, *J.*, 1936, 393).

The moments induced in the *p*-chlorine atom of the 3-*p*-chlorophenyl group by the sydnone group moment, and induced in the sydnone group by the corresponding carbon–chlorine dipole are small, being 0·045 and 0·065 D, respectively. Moreover, they are opposed: so the net induced moment is only 0·02 D. Were the $Ph–N_{(3)}$ bond to be collinear with the sydnone moment (μ_S) as supposed above, the actual interaction moment would have to be 0·08 or 0·15 D (see p. 1488). Clearly, therefore, it is due to other causes—probably to mesomeric interaction. A parallel case is *p*-chloronitrobenzene, wherein a difference of 0·15 D is found between the observed * and the calculated moment. This is such as to correspond to a smaller moment of substitution of hydrogen by chlorine, *i.e.*, of 1·40 D. Here, also, the interaction moment to be expected from simple electrostatic induction is very small, being only 0·005 D and in the opposite direction to the observed one. The moment postulated for this interaction is therefore plausible; but it cannot be given a firm quantitative basis.

The second type of suspected interaction is not merely impossible to calculate, but is even difficult to understand qualitatively. The vector diagrams for the modified first series of moments and for either the modified second series or the third series show that $\angle ABF$ is greater in the former than in the latter—see Fig. F, where BF represents the PhCl vector for the first series and BF' that for the last two. The same would be true of two triangles ACE and ACE'. If the former series is normal, as is indicated by the reasonableness of the results (see above), there is therefore an interaction moment FF' (about 0·4 D) in both the 3 : 4-diphenylsydnone series when substitution is effected in the *para*-position of the 4-phenyl group, and this is the same whether the substitutent group is chlorine or methyl. If, on the other hand, the last two series are normal, as their consistency indicates, then there must be an interaction moment $F'F$ in the first series when the 4-hydrogen atom is substituted by chlorine.

The former alternative moment FF' is in the right direction for one electrostatically induced by the main sydnone moment (along AB, which makes an angle of about −15° to −20° to the $N_{(2)}–O_{(1)}$ axis) in a *para*-substituent on the 4-phenyl group: but such a moment, and a larger one at that, should also be induced in a substituent directly on the $C_{(4)}$ atom, so electrostatic induction would probably *invert* F and F'. A mesomeric mechanism by which electrons are transferred from the *para*-substituent, irrespective of whether it is Cl or CH_3, towards the 3-phenyl group seems unlikely. A moment FF' in the direction shown is therefore difficult to explain.

An opposite moment, $F'F$, could be explained by the chlorine atom substituted directly on $C_{(4)}$ acting as an electron source which, by a plausible mesomeric process, increases the main sydnone moment. The interposition of a phenyl group should reduce this process in the 3 : 4-diphenylsydnone derivatives. The fact that 4-nitro-3-phenylsydnone has a moment of only 6·18 D, instead of the 7·19 D to be expected for the geometry of triangle ABF for the first (3-phenylsydnone) series, supports this view; because the nitro-group is more electrophilic than the chlorine atom. Were it correct, however, the reason why the value for $\angle ABF'$ is so small, and why therefore the results for the intervalency angle and for μ_π are anomalous, would still be to seek.

For the sake of completeness we may briefly consider the possibility that some of the variation of derived intervalency angle is due to the effect of solvent on the observed dipole

* Mr. M. F. Saxby (personal communication) finds a value of 2·61 D for this substance which has previously been measured with varying results; cf. Wesson's "Tables of Electric Dipole Moments," M.I.T. Press, 1948.

moments. Frank remarked (see Sutton and Hampson, *loc. cit.*) that if, in any one solvent the moment of the parent compound and the substitution moments are definite in magnitude and direction, implying that the solvent effect shall not disturb any geometric relations assumed between the moments and their atomic framework, then calculations of intervalency angles from the changes in moment caused by substitution are not affected by solvent. These conditions appear to be satisfied, at least to a first approximation, if one may judge from the results for the intervalency angle in diphenyl ether. From the measurements given by Sutton and Hampson (*loc. cit.*) for the *p*-bromo-derivatives, and those of Leonard and Sutton (*J. Amer. Chem. Soc.*, 1948, **70**, 1568) for the *p*-fluoro-derivatives, the best value for the intervalency angle Ph–O–Ph from solution measurements is 121° ± 4° if atom polarisation is ignored, and 123·5° ± 7° if it is allowed for as in the former paper. The vapour-phase measurements by Coop and Sutton (*J.*, 1938, 1869) * give 124° ± 5° for this angle. There is also a value of 118° ± 3° from electron-diffraction work (Maxwell, Hendricks, and Mosley, *J. Chem. Phys.*, 1935, **3**, 699). The present application is of the same type; so the anomalies are probably not due to this cause.

Although there emerges no comprehensive and exact explanation of all the dipole moment evidence, the following conclusions seem justified: (*a*) The Ph–$N_{(3)}$ valency in 3-phenylsydnone, by a fortunate chance, is very nearly collinear with the main sydnone moment; and it therefore lies within 5° or so of the plane of the sydnone ring. (*b*) The angle between the Ph–$N_{(3)}$ and the $C_{(4)}$–X valencies is probably not greater than 80°; so the latter valency is itself not more than 10° out of the plane of the sydnone ring. (*c*) The magnitude of μ_π is about 4·8 D. (*d*) The direction of μ_π is roughly parallel to the $N_{(2)}$–$O_{(1)}$ bond. Because of the complexity of the arguments, clear limits of error cannot be ascribed.

The conclusions support the meso-ionic structure (II), and agree reasonably well with theoretical calculations based thereon.

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The Physical Chemistry Laboratory, Oxford. [*Received, October 23rd*, 1952.]

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303. *The Chemotherapy of Tuberculosis. Part IV.*† *Some N-Substituted Nicotinamides and Nicotinamidines.*

By J. N. Baxter and J. Cymerman-Craig.

Two parallel series of six *N*-aryl-nicotinamides and -nicotinamidines have been prepared. Their basic dissociation constants have been determined potentiometrically in 50% alcoholic solution: these bear no visible relations to the relative antituberculous activities.

Because of the well-known antituberculous activity of nicotinamide and its *N*-substituted derivatives, and the relation of basic strength to antibacterial action, the effect of an increase in the basicity of compounds related to nicotinamide on their antituberculous activity has been investigated. A series of six *N*-aryl-nicotinamidines, 3-C_5H_4N·C(:NH)·NHAr, was prepared by Oxley and Short's method (*J.*, 1946, 147), the corresponding nicotinamides being readily obtained for comparison from nicotinoyl chloride and the appropriate amine.

Potentiometric titration in 50% alcoholic solution at 20° ± 1° (procedure: Carswell, Cymerman, and Lyons, *J.*, 1952, 430) was used to obtain the pK_a values (see Table 1). Amides were titrated with N/20-hydrochloric acid, while for the amidines the hydrochlorides

* There is a misquotation in this paper of solution results given previously by Sutton and Hampson (*loc. cit.*). † Part III, *J.*, 1951, 2342.

(or, in the case of benzamidine, the benzenesulphonate) were titrated with N/20-sodium hydroxide. Results were corrected for hydrogen- or hydroxyl-ion concentration. It is seen that the pK_a of nicotinamide lies close to that of the similarly constituted 3-acetylpyridine, in accord with the $+I$ and $+E$ effect of these groups, and the substitution of a phenyl or 4-diphenylyl group for an amide-hydrogen atom lowers the pK_a by 0·39 and 0·66 unit respectively. In both nicotinamidine and benzamidine, substitution of an amino-hydrogen atom by the 4-diphenylyl group reduces the pK_a by 3 units.

Antituberculous activities *in vitro* (Table 2) have been kindly determined by Pro-

TABLE 1. *Ionisation constants.*

Compound	pK_a at 20° ± 1°	Solvent	Compound	pK_a at 20° ± 1°	Solvent
Pyridine	5·19	Water [1]	Nicotinamidine	9·65	50% Alcohol
Nicotinic acid	3·55	,, [2]	*N*-4-Diphenylylnicotinamidine	6·63	,,
3-Acetylpyridine	3·18	,, [1]	Benzamidine	11·6	Water [3]
Nicotinamide	3·15	50% Alcohol		11·23	50% Alcohol
Nicotinanilide	2·76	,,	*N*-4-Diphenylylbenzamidine	8·10	,, [4]
N-4-Diphenylylnicotinamide	2·49	,,			

[1] Hall and Sprinkle, *loc. cit.*; values at 25°. [2] Basic dissociation constant; Hughes, Jellinek, and Ambrose, *J. Phys. Colloid Chem.*, 1949, **53**, 410. [3] Albert, Goldacre, and Phillips, *J.*, 1948, 2240. [4] Carswell, Cymerman, and Lyons, *loc. cit.*

TABLE 2.

N-Substituent	Nicotinamides, activity * with 10% serum	Nicotinamides, activity * without serum	Nicotinamidines, activity * with 10% serum	Nicotinamidines, activity * without serum
p-Ethoxyphenyl	—	—	<2000	<2,000
p-Chlorophenyl	2,000	4,000	<2000	<2,000
*p-cyclo*Hexylphenyl	<8,000	<8,000	8000	16,000
4-Diphenylyl	<8,000	<8,000	4000	8,000
p-Phenoxyphenyl	16,000	32,000	4000	8,000
2-Dibenzofuryl	<8,000	<8,000	<2000	<2,000
None	<125	500	<125	125

* Highest dilution expressed as 1/molarity of the substance completely inhibiting growth of *Mycobact. tuberculosis* (H. 37 Rv) in Youmans's medium after 14 days at 37°.

fessor S. D. Rubbo, and a full account of the bacteriological aspects will be given elsewhere. Although the *N*-substituted compounds greatly exceed the parent substances in activity, the highest activity recorded is of a low order, and no clear relation appears between ionisation and activity in this series. Activities were decreased by the presence of serum.

Prolonged evaporation of an aqueous solution of *N*-*p*-chlorophenylnicotinamidinium toluene-*p*-sulphonate at 100° gave *N*-*p*-chlorophenylnicotinamide, accompanied by some of the amidine salt. Such hydrolysis of an amidine in neutral solution may be ascribed to the presence of some free amidine base. The 4-diphenylyl-amidine has pK_a only 6·63 at 20° in 50% alcohol, and the base-weakening influence of substituents is in the order Cl>Ph>OEt; *e.g.*, *p*-chloroaniline, 4-aminodiphenyl, and *p*-phenetidine have pK_a 4·0, 4·27, and 5·25 respectively at 25° in water (Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3472). The *p*-chlorophenyl-amidine will thus have pK_a less than 6·63 at 20° in 50% alcohol, so that a considerable proportion of free amidine will exist in neutral solution, giving rise to the observed hydrolysis. Neutral hydrolysis also occurred with the *p*-ethoxyphenyl-amidine, but only 1% of amide was obtained in this case; the *p*-ethoxyphenyl analogue will have pK_a greater than 6·63 under the same conditions, and the proportion of free base present will therefore be much smaller.

It is seen from Table 1 that the basic strengths of nicotinamidines are 1·5 pK units lower than those of the corresponding benzamidines; this appears to be due to the general electron-withdrawing effect of the ring-nitrogen atom in the former.

EXPERIMENTAL

N-Substituted Nicotinamides.—A solution of nicotinoyl chloride hydrochloride (0·01 mole) in dry pyridine (5 c.c.) was mixed with a solution of the amine (0·01 mole) in dry pyridine (20 c.c.), and the next morning poured into ice-water (150 c.c.). The precipitate crystallised from chloroform or alcohol, giving the *amides* in 55—65% yield as needles or prisms (see Table 3).

N-*Substituted Nicotinamidines.*—The amine toluene-*p*-sulphonate (0·05 mole) and 3-cyanopyridine (0·05 mole plus 15% excess) were heated at 200° for 1·5—2·5 hours, the mixture extracted with ether, and the ether-insoluble solid extacted with boiling water. The amidine salt separated from the aqueous filtrate on cooling or on concentration *in vacuo*, and crystallised from water or *iso*propanol in plates or needles of the *amidinium toluene*-p-*sulphonates* in 25—35% yield (see Table 4). The free base was obtained by basifying an ice-cold aqueous solution of the pure salt. Crystallisation from chloroform–light petroleum (b. p. 40—60°) afforded the amidines as plates or prisms (see Table 5).

TABLE 3. N-*Substituted nicotinamides.*

			Found (%)			Requires (%)		
N-Substituent	M. p.	Formula	C	H	N	C	H	N
p-*Chlorophenyl*	169·5—170°	$C_{12}H_9ON_2Cl$	61·9	4·1	11·9	61·9	3·9	12·05
p-cyclo*Hexylphenyl*	203—203·5	$C_{18}H_{20}ON_2$	77·25	7·15	10·45	77·1	7·2	10·0
4-*Diphenylyl* [1]	217	$C_{18}H_{14}ON_2$	79·0	5·25	10·6	78·8	5·15	10·2
p-*Phenoxyphenyl*	149·5—150	$C_{18}H_{14}O_2N_2$	74·6	4·95	9·65	74·5	4·85	9·65
2-*Dibenzofuryl*	220	$C_{18}H_{12}O_2N_2$	74·65	4·05	10·0	75·0	4·2	9·75

[1] The *hydrochloride* formed plates (from alcohol), m. p. 267° (Found: C, 69·3; H, 4·95; N, 8·5. $C_{18}H_{14}ON_2,HCl$ requires C, 69·55; H, 4·85; N, 9·0%).

TABLE 4. N-*Substituted nicotinamidinium toluene*-p-*sulphonates.*

			Found	Requires
N-Substituent	M. p.	Formula	N (%)	N (%)
p-*Ethoxyphenyl*	220°	$C_{21}H_{23}O_4N_3S$	9·8 [1]	10·15
p-cyclo*Hexylphenyl*	178	$C_{25}H_{29}O_3N_3S$	— [2]	—
4-*Diphenylyl*	213	$C_{25}H_{23}O_3N_3S$	9·2, 9·45	9·45
p-*Phenoxyphenyl*	170	$C_{25}H_{23}O_4N_3S$	9·3	9·1
2-*Dibenzofuryl*	213	$C_{25}H_{21}O_4N_3S$	9·1	9·15

[1] Found: S, 7·65. Requires S, 7·75%. [2] Found: C, 66·7; H, 6·7. Requires C, 66·5; H, 6·5%.

TABLE 5. N-*Substituted nicotinamidines.*

			Found (%)			Requires (%)		
N-Substituent	M. p.	Formula	C	H	N	C	H	N
p-*Ethoxyphenyl*	128—129°	$C_{14}H_{15}ON_3$	69·4	6·1	17·5	69·7	6·25	17·4
p-*Chlorophenyl*	190	$C_{12}H_{10}N_3Cl$	61·9	4·15	17·5	62·2	4·35	18·1
p-cyclo*Hexylphenyl*	172	$C_{18}H_{21}N_3$	—	—	14·8	—	—	15·0
4-*Diphenylyl*	162·5	$C_{18}H_{15}N_3$	78·9	5·7	15·0	79·1	5·5	15·4
p-*Phenoxyphenyl*	163—164	$C_{18}H_{15}ON_3$	—	—	14·1	—	—	14·5
2-*Dibenzofuryl*	217·5	$C_{18}H_{13}ON_3$	—	—	14·4	—	—	14·6

Neutral Hydrolysis of Amidines.—(*a*) Evaporation of an aqueous solution of *N*-*p*-chlorophenylnicotinamidinium toluene-*p*-sulphonate at 100° afforded a solid (A), part of which after repeated crystallisation gave *N*-*p*-chlorophenylnicotinamide, m. p. 170° (Found: N, 12·0. Calc. for $C_{12}H_9ON_2Cl$: N, 12·0%), undepressed on admixture with an authentic sample. Part of (A) was basified at 0° and crystallisation of the base from chloroform gave fractions (i) and (ii). A small fraction (i) consisted of the amidine, m. p. and mixed m. p. 189°. The *amidine dihydrochloride*, crystallised from methanol–ether, had m. p. 258—259° (decomp.) (Found: N, 13·8; equiv., 156. $C_{12}H_{10}N_3Cl,2HCl$ requires N, 13·8%; equiv., 152). The *dipicrate*, plates (from alcohol), had m. p. 166° [Found: N, 17·9; equiv. (by titration with sodium hydroxide in presence of thymolphthalein), 339. $C_{12}H_{10}N_3Cl,2C_6H_3O_7N_3$ requires N, 18·25%; equiv., 345]. Fraction (ii), m. p. 151—152°, gave a mixture of two picrates, one of which had m. p. 166°, undepressed on admixture with the amidine dipicrate above, while the other crystallised from alcohol in orange prisms, m. p. 204—206° of N-p-*chlorophenylnicotinamide picrate* (Found: C, 47·2; H, 2·3; N, 14·4. $C_{12}H_9ON_2Cl,C_6H_3O_7N_3$ requires C, 46·8; H, 2·6; N, 15·2%) (m. p. undepressed by an authentic sample).

(*b*) Evaporation of an aqueous solution of *N*-p-ethoxyphenylnicotinamidinium toluene-*p*-sulphonate gave (i) the amidine toluene-*p*-sulphonate in 35% yield (see Table 3) and (ii) an oil which solidified and crystallised from *iso*propanol to give *N*-*p*-ethoxyphenylnicotinamide (1%), m. p. 171—172° (Found: C, 68·7; H, 5·9; N, 11·8. Calc. for $C_{14}H_{14}O_2N_2$: C, 69·4; H, 5·8; N, 11·6%). Lanfranchi (*Chem. Abs.*, 1947, **41**, 454) gives m. p. 170—171°.

Materials for pK_a *Determinations.*—Nicotinamide: plates, m. p. 129° (lit., m. p. 129—131°). Nicotinanilide: m. p. 119—120° [from benzene–light petroleum (b. p. 40—60°)] (Badgett,

Provost, Ogg, and Woodward, *J. Amer. Chem. Soc.*, 1945, **67**, 1135, give m. p. 127°). The *hydrochloride* crystallised from alcohol in needles, m. p. 201·5—202° (Found: C, 61·2, 61·3; H, 4·7, 4·8; N, 11·5. $C_{12}H_{10}ON_2,HCl$ requires C, 61·4; H, 4·75; N, 11·9%).

Nicotinamidine: the hydrochloride crystallised from *iso*propanol–ether and had constant m. p. 186—187° (Barber and Slack, *J. Amer. Chem. Soc.*, 1944, **66**, 1607, give m. p. 190°).

The authors gratefully acknowledge their indebtedness to Professor S. D. Rubbo and Miss B. Pierson for kindly undertaking the bacteriological tests. Microanalyses are by Mrs. E. Bielski and the C.S.I.R.O. Microanalytical Laboratory. This work was carried out under the auspices of the National Health and Medical Research Council, to whom thanks are due for financial assistance.

Organic Chemistry Department, University of Sydney. [*Received, November 3rd, 1952.*]

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304. *Infusible White Precipitate: Some New Evidence as to its Structure, from a Study of its Thermal Decomposition.*

By D. R. Glasson and S. J. Gregg.

Measurements have been made of (*a*) the rate of thermal decomposition, (*b*) the total loss in weight (due to evolution of ammonia), and (*c*) the dissociation pressure, on the compounds $HgCl_2,2NH_3$, $HgI_2,2NH_3$, and $3HgI_2,4NH_3$; and of (*a*) and (*b*) on $HgCl_2,2C_5H_5N$ and infusible white precipitate. From (*a*) the energy of activation E, and from (*c*) the heat of dissociation $-\Delta H$, have been calculated for the loss of ammonia (or of pyridine) from the compounds. Comparison of the value of E for infusible white precipitate with the values of E and of $-\Delta H$ for the other compounds shows that Britton and Wilson's formula $HgO,HgCl_2,2NH_3$ is more probable than the customary Franklin formula $NH_2{\cdot}HgCl$ or the older Rammelsberg formula NHg_2Cl,NH_4Cl. This conclusion is supported by the data under (*b*) and also by the fact that the content of "basic" mercury (HgO) in infusible white precipitate is unaltered by heating.

The formation of the complex $HgCl_2,0{\cdot}67NH_3$ in the dry way does not appear to have been reported before.

The structure now usually assigned to infusible white precipitate is $NH_2{\cdot}HgCl$ (I) (Franklin, *J. Amer. Chem. Soc.*, 1907, **29**, 35; Partington, "General and Inorganic Chemistry," 1949, p. 402), rather than the earlier formula NHg_2Cl,NH_4Cl (II) (Rammelsberg, *J. pr. Chem.*, 1883, **38**, 558; Pecci, *Gazzetta*, 1889, **19**, 509; 1890, **20**, 485; *Z. anorg. Chem.*, 1899, **21**, 362). Britton and Wilson (*J.*, 1932, 2550; 1933, 601, 1043), however, have brought forward considerable evidence to show that the constitution of the substance is $HgO,HgCl_2,2NH_3$ (III) and that it represents a particular member of a general series $x HgO,(1-x)(HgCl_2,2NH_3)$ formed by the hydrolysis (during preparation) of fusible white precipitate, $HgCl_2,2NH_3$.

Britton and Wilson's arguments were based on conductometric and electrometric titrations and analysis; and it was thought that further evidence should be obtainable by a study of the thermal decomposition of the substance in comparison with that of related substances of known constitution. The reference substances chosen were the diammines of mercuric chloride and iodide, and the dipyridinium compound of mercuric chloride; the quantities measured were the energies of activation and of decomposition for the loss of ammonia (or of pyridine), and the total weight of ammonia (or of pyridine) lost in each of the stages of the decomposition. The results obtained support Britton and Wilson's formula (III).

Diamminomercuric Iodide, $HgI_2,2NH_3$.—When heated, this compound loses its ammonia in two stages (François, *Compt. rend.*, 1899, **129**, 296; 1900, **130**, 572):

$$3(HgI_2,2NH_3) \longrightarrow 3HgI_2,4NH_3 + 2NH_3 \quad \ldots\ldots\ldots \text{(i)}$$

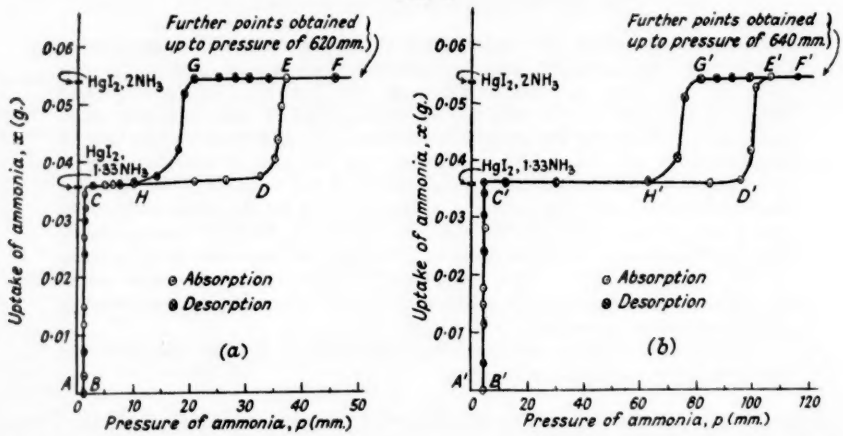
and

$$3HgI_2,4NH_3 \longrightarrow 3HgI_2 + 4NH_3 \quad \ldots\ldots\ldots \text{(ii)}$$

To determine the heat of dissociation $-\Delta H$ for each of these reactions, the dissociation pressure corresponding to each of the systems (i) and (ii) was measured at 20° and at 40°, and the value of $-\Delta H$ calculated by van't Hoff's isochore: x was plotted against p, where x is the content of ammonia in the solid phase, and p the pressure of ammonia in equilibrium with the solid phase. From the stepped isotherms obtained, the value of the dissociation pressure p_d could be read off.

From the experimental point of view the task is essentially one of determining a sorption isotherm, and a sorption technique is appropriate. The electrical sorption balance already described by one of us (*J.*, 1946, 561) was used, together with suitable attachments which permitted the balance case to be evacuated and gas to be admitted to it in a controlled manner (Gregg and Sing, *J. Phys. Coll. Chem.*, 1951, **55**, 597); the glass limb surrounding the bucket containing the solid was immersed in a thermostat at the appropriate temperature, and the pressure p was read on a mercury manometer. The resultant isotherms at 20° and 40° are represented in Fig. 1, where the horizontal steps *GEF* in (*a*) and *G'E'F'* in (*b*) correspond closely to $HgI_2,2NH_3$, and *CHD* and *C'H'D'* to $3HgI_2,4NH_3$. That the latter steps are not absolutely horizontal is probably due to slight physical adsorption.

FIG. 1.



The reversibility of each reaction was tested by determining the curve both when p was successively increased (p_a), and when it was similarly decreased (p_b); for each of the branches *BC* and *B'C'* corresponding to reaction (ii), p_a and p_b agreed within 0·3 mm.; the dissociation pressure p_d [$=(p_a + p_b)/2$] is 1·3 mm. at 20° and 5·5 mm. at 40°, leading to a value $-\Delta H = 13{\cdot}2$ kcal. mole^{-1} [cf. 12·9 kcal. mole^{-1} from the data of François (*loc. cit.*)].

With reaction (i) p_a and p_b differed widely and the steps *GH* and *G'H'* were not accurately vertical, indicating hysteresis effects. Taking p_d as the value of p_a or of p_b half-way between *G* and *H* or between *G'* and *H'*—where the isotherms are of maximum slope—gives *two* values for p_d at each temperature [*viz.*, 18·5 and 35·5 mm. at 20° and 75·0 and 100 mm. at 40°), and two estimates of $-\Delta H$, *viz.*, 10·0 kcal. mole^{-1} from p_a and 13·0 kcal. mole^{-1} from p_b [cf. 11·4 kcal. mole^{-1} from the data of François (*loc. cit.*)].

For calculation of the energy of activation E, it was necessary to determine the kinetics of each of the isothermal decompositions (i) and (ii) at two neighbouring temperatures. By analysis of the resultant curves of "weight decomposed" against "time" a measure of the *rate* of the decomposition at each temperature can be obtained; and the energy E can then be calculated from the usual Arrhenius formula, $[RT_1T_2/(T_2 - T_1)] \ln r_2/r_1$ (r_2 = rate at temperature T_2, r_1 = rate at temperature T_1).

The apparatus was exactly as before, a specimen of the diammine being contained in the bucket. To minimise the variation in "activity" of the solid from one run to another, the diammine for each run was obtained by ammoniating *in situ* the mercuric iodide from

the previous run by exposure to ammonia at 1 atm. for 12 hr. at the temperature of the run. The sample for the first run was obtained by decomposing and reammoniating a sample of the ammine prepared in the wet way.

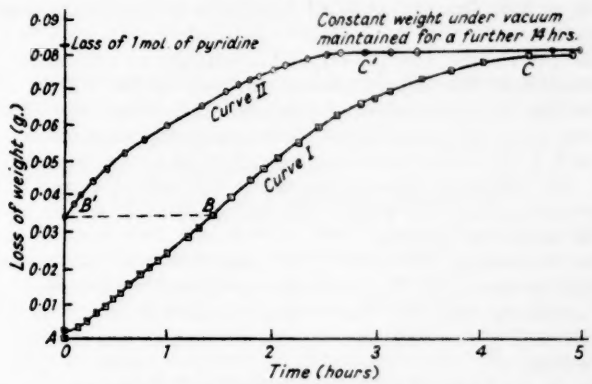
During stage (i) the pressure of ammonia in the apparatus was kept just above the dissociation pressure of stage (ii) in order to prevent the intrusion of the latter; during stage (ii) the system was kept evacuated in the usual manner by a mercury-diffusion pump.

Analysis of the curve of " loss of weight " against " time " showed that the decomposition obeyed with reasonable accuracy, over the range 10—90% of the complete reaction, the equation

$$(w/w_0)^{1-n} = -kt + a \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where w_0 and w are the weights of NH_3 present in the sample initially and at time t respectively, and a is a constant close to zero. Writing equation (1) in the differential form $-\mathrm{d}(w/w_0)/\mathrm{d}t = (k/1-n)(w/w_0)^n$, one sees that the order of the reaction is n. The index $(1 - n)$ was evaluated by plotting $(w/w_0)^{1-n}$ for a series of values of $(1 - n)$ and choosing that which gave the best straight line (cf. Britton, Gregg, and Winsor, *Trans. Faraday Soc.*, 1952, **48**, 63); this gave $(1 - n) = 0{\cdot}17 \pm 0{\cdot}04$, corresponding to an order of $0{\cdot}83 \pm 0{\cdot}04$. It thus seems probable that the reaction proceeds at an advancing interface, which ideally would give $n = 0{\cdot}67$, but is liable to disturbing effects which cause deviations of n from this ideal value (cf. *idem, ibid.*; Gregg and Razouk, *J.*, 1949, S 36). The presence of an interface was, indeed, visible to the naked eye in partly decomposed samples.

FIG. 2.



The value of k can be read off as the slope of the plot of equation (1), and the value of E calculated from the ratio k_{40}/k_{20} $(= r_2/r_1)$ by the Arrhenius expression. This gave $E_{\mathrm{i}} = 17{\cdot}4$ kcal. mole^{-1} for reaction (i), and $E_{\mathrm{ii}} = 17{\cdot}5$ kcal. mole^{-1} for reaction (ii).

Dipyridinomercuric Chloride, $HgCl_2$,2py.—With this substance the measurements were confined to the kinetics of decomposition. Four runs were carried out, two at 20° and two at 40°, with samples weighing 0·5000 g. each. The curve for the first experiment at 20° is given in Fig. 2 (Curve I), whence it will be seen that the flattening at C occurs when the loss of weight corresponds closely to the formation of the monopyridinium derivative $HgCl_2$,py. [This was confirmed by analysis of the residue of the experiment (Found: Hg, 56·9; Cl, 20·1; C_5H_5N, by titration, 22·7. Calc. for $HgCl_2,C_5H_5N$: Hg, 57·2; Cl, 20·2; C_5H_5N, 22·6%).] The residue had m. p. 194—195° (cf. 193—194° for $HgCl_2,C_5H_5N$ prepared as described on p. 1498).

The sigmoid character of Curve I, Fig. 2, indicates that decomposition nuclei are being formed over the initial part, AB, where the slope is increasing with time (Garner, *J.*, 1930, 47; Hume and Colvin, *Proc. Roy. Soc.*, 1931, **132**, *A*, 548). At B the rate begins to diminish, indicating that nucleation is drawing to an end, a suggestion that was confirmed by a further experiment: a sample of the $HgCl_2$,2py was rapidly nucleated by exposing it to

vacuum at 60° till the fraction of weight lost was the same as that at *B* in Curve I; the solid was then rapidly cooled to 20° in presence of air, and the system rapidly evacuated, whereupon decomposition recommenced. The curve obtained (Curve II) for the decomposition *in vacuo* at this lower temperature could be almost perfectly superposed on the portion *BC* of Curve I, showing that the effect of nucleation on the rate of decomposition can be ignored once the point of inflection *B* has been passed. In the remaining experiments, therefore, the solid was activated by heating it *in vacuo* for a short time at 60°, and admitting air and cooling it to 20° (or 40°) before pumping was recommenced.

The decomposition—once the point of inflection has been passed—is again represented by equation (1), with $n = 0{\cdot}67 \pm 0{\cdot}03$. The energy of activation calculated from the values of k at 20° and at 40° is $E = 15{\cdot}3$ kcal. mole^{-1}.

An attempt was made to determine the value of E for the loss of quinoline from diquinolinomercuric chloride, $HgCl_2,2C_9H_7N$. Similar results were obtained, but whereas the value of n was *ca.* 0·67 at 60°, it was *ca.* 0·80 at 80°. The change of index made it impossible to insert k_2/k_1 for r_2/r_1 in the Arrhenius equation; instead r_2 and r_1 were taken as equal to the slopes at 40° and 20°, respectively, of the curve of w against t for a given fraction (w/w_0) decomposed. The value of E varied considerably according to the amount decomposed; consequently, the true value of this quantity is uncertain, but it is satisfactory that the range of values found—22·3—15·4 kcal. mole^{-1} as the loss rose from 0·25 to 0·90 mole of quinoline per mole of $HgCl_2$—is of the same order as E for the pyridinium compound.

Fusible White Precipitate, $HgCl_2,2NH_3$.—The energy of activation for the loss of ammonia was determined from measurements on the sorption balance of the isothermal rate of loss of weight at a succession of temperatures. Since the product of reaction ($3HgCl_2,2NH_3$) was appreciably volatile at the experimental temperatures, the " bucket " was now made with a drawn-out neck long enough to be above the level of the water in the thermostat; the sublimate then condensed in the neck (plugged with glass-wool as an additional precaution) and its weight was still registered, so the loss in weight was entirely due to the ammonia evolved.

Decomposition *in vacuo* at 147°, 128°, 125°, and 105° gave a curve of loss of weight against time which became horizontal at a loss corresponding to *two-thirds* (not one-half) of the original ammonia content; the residue thereafter slowly sublimed unchanged (condensing in the neck of the container) so that no further loss of weight was registered. The reaction was thus:

$$3(HgCl_2,2NH_3) \longrightarrow 3HgCl_2,2NH_3 + 4NH_3 \quad . \quad . \quad .

times lowered to T_1—readings of pressure were again taken to constancy, and the temperature moved back to T_2. The second pressure at T_2 agreed satisfactorily with the first at pressures above 20 mm. (3—4 hr. being required for equilibration), but at lower pressures the two values of p at a given temperature, T_2, differed by 5 mm. or so, even when (after some 5 hr.) the pressure had become seemingly constant. Accordingly, the values of p_d are not very reliable in the lower pressure range, the sublimation of the product $3HgCl_2,2NH_3$ being a possible source of error.

The plot of p against $1/T$ (p being taken as the mean of the values obtained before and after alteration of temperature) gives a good straight line except at the low-pressure end, where as expected there is considerable scatter. From the slope of this line the value $-\Delta H = 21{\cdot}4$ kcal. mole^{-1} is obtained.

Infusible White Precipitate.—The rate of decomposition of infusible white precipitate was studied in exactly the same manner as for fusible white precipitate at temperatures of 148°, 155°, and 170°; two runs were conducted *in vacuo* at each temperature, the duplicates showing excellent agreement. In each case there were again indications of a " nucleation " effect in that the rate of decomposition initially increased with time for a short period. The results again fitted with moderate accuracy an equation of the form of equation (1); but in view of the disturbance introduced by the nucleation effect, it was decided to calculate E from the rate r_{40} at 40% decomposition, where the disturbing effect had disappeared, as judged by the form of the isotherm. A plot of the log r_{40} against $1/T$ gave a good straight line, whence the energy of activation was calculated as $E = 20{\cdot}0$ kcal. mole^{-1}.

The total loss of weight in the experiment varied between 3·15 and 3·25%. This corresponds closely to the calculated weight of ammonia released according to the equation :

$$HgO,HgCl_2,2NH_3 \longrightarrow HgO,HgCl_2,NH_3 + NH_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (iv)$$

viz., 3·27%. Franklin's formula would give

$$3NH_2{\cdot}HgCl \longrightarrow NHg_2Cl + HgCl_2 + 2NH_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (v)$$

and this would require a loss, *viz.*, 4·50%, much larger than the experimental figure. Moreover, mercuric chloride sublimes rapidly in air at 150° and *in vacuo* at *ca.* 100°; yet in the present experiments the weight of sublimate caught in the neck of the container was a mere 5% of the initial weight of the sample and this could be accounted for as $HgCl_2,0{\cdot}67NH_3$ formed from the small content of fusible white precipitate present as impurity. Actually, Franklin's formula is often given as $NH_2{\cdot}HgCl,xH_2O$ in order to bring it into line with the analytical results; it is seen that the loss of weight would then be even greater than 4·50% as it would include the water.

It was hoped to determine the energy of activation for the loss of the remaining ammonia from infusible white precipitate, after completion of reaction (iv), and the residue from the earlier experiments was accordingly decomposed *in vacuo* at 200° and at 250°, on the sorption balance. Unfortunately, extensive sublimation occurred at both temperatures: in the 200° experiment the composition of the sublimate was very close to $HgCl_2,0{\cdot}67NH_3$, whereas for 250° it was $HgCl_2,0{\cdot}83NH_3$ in one experiment and $HgCl_2,0{\cdot}95NH_3$ in the other, indicating that the sublimate was now a mixture of $HgCl_2,0{\cdot}67NH_3$ with $HgCl_2,2NH_3$. Owing to this complication it was not possible to calculate the value of E; but the experiments provide further, indirect, support for Britton and Wilson's formula, inasmuch as neither Franklin's nor Rammelsberg's formula can account for the formation of an ammoniated sublimate when the solid product of reaction (iv) is heated *in vacuo*.

Additional evidence is furnished by the results of determinations of the content of " basic " mercury (say Hg_B) before and after the decomposition of infusible white precipitate *in vacuo*; the method used was treatment with potassium iodide and titration with acid of the liberated potassium hydroxide and ammonia (cf. Britton and Wilson, *J.*, 1933, 9) :

$$HgO + 4KI + H_2O \longrightarrow K_2HgI_4 + 2KOH$$

$$xHgO,(1-x)HgCl_2,2NH_3 + (2-x)H_2O + 4KI \longrightarrow K_2HgI_4 + 2xKOH + 2(1-x)NH_4OH + 2(1-x)KCl$$

The content of Hg_B in a 2·000-g. specimen was 0·797 g. before, and 0·790 g. after, such decomposition at 155°; a second specimen, also 2·000 g., gave 0·773 g. of Hg_B after decomposition at 250°. Thus within experimental limits the content of basic mercury is unchanged by the decomposition *in vacuo*, and this strongly supports the " basic chloride " type of constitution, $HgO,HgCl_2,2NH_3$.

Conclusion.—The values now obtained for E and $-\Delta H$ (kcal. per mole of NH_3) are summarised herewith :

(i)	$3(HgI_2,2NH_3) \longrightarrow 3HgI_2,4NH_3 + 2NH_3$	$E = 17{\cdot}4$, $-\Delta H = 10{\cdot}0$—$13{\cdot}0$
(ii)	$3HgI_2,4NH_3 \longrightarrow 3HgI_2 + 4NH_3$	$E = 17{\cdot}5$, $-\Delta H = 13{\cdot}2$
(iii)	$HgCl_2, py_2 \longrightarrow HgCl_2, py + py$	$E = 15{\cdot}3$
(iv)	$3(HgCl_2,2NH_3) \longrightarrow 3HgCl_2,2NH_3 + 4NH_3$	$E = 11{\cdot}4$, $-\Delta H = 26{\cdot}4$
(v)	Loss of $1NH_3$ from infusible white precipitate	$E = 20{\cdot}0$.

The value of E for infusible white precipitate is thus of the same order as the value of $-\Delta H$ and of E for reactions (i)—(iv) in which either ammonia, or a substituted ammonia, is released by the rupture of a co-ordinate link between a mercury atom and a nitrogen atom. Moreover, the values of $-\Delta H$ just quoted are of the same order as those for the loss of ammonia from the ammines of the halides of metals other than mercury. They are too numerous to quote in detail, but may be summarised as follows (in kcal. mole^{-1}) : PbX_2, 11·3—15·6; ZnX_2, 19·4—25·0; $CdCl_2$, 18·6; SnX_2, 13·3—27·2; $CaCl_2$, 15·0; CuX, 10·4—16·7; AgX, 10·7—11·1 (X = Cl, Br, or I) (cf. Biltz *et al.*, *Z. phys. Chem.*, 1909, **67**, 578; *Z. anorg. Chem.*, 1920, **114**, 174; 1921, **119**, 27; 1922, **124**, 230; 1923, **129**, 161, 230; **130**, 93; Glasson, Thesis, London, 1949, p. 169). Hart and Partington (*J.*, 1943, 104) give results for the ammines of various halides of Ca, Ba, Ni, Li, Na, Fe^{II}, Mn^{II}, and Cu^{II}, and 31 values lie between 9·86 and 19·38, one being 24·3.

These facts support formula (III) as against (I); if the latter were correct, the value of E for infusible white precipitate should lie distinctly higher than the values of E and of $-\Delta H$ for the ammines, since the loss of an ammonia molecule would involve an interaction between two NH_2 groups, attached to separate mercury atoms, and should indeed be comparable with that for the loss of ammonia from a metallic *amide*. There are no data permitting the calculation of E for the decomposition of metal amides, but figures are available for the heats of formation (cf. I.C.T., Vol. 5, pp. 196 *et seq.*), whence $-\Delta H$ may be calculated for the amides of Ca, Sr, Ba, and Li as 30·3, 27·8, 25·4, and 35·2 kcal. mole^{-1}, respectively. As expected, these are higher than any of the values quoted for the ammines, and considerably higher than most of them. For the same metal, Ca, the difference is particularly striking : the value for the amide, 30·3 kcal. mole^{-1}, is nearly twice as high as that for the ammine in the reaction $CaCl_2,2NH_3 \longrightarrow CaCl_2,NH_3 + NH_3$, *viz.*, $-\Delta H = 15{\cdot}3$ kcal. mole^{-1} (cf. Hüttig, *Z. anorg. Chem.*, 1922, **123**, 317).

The data for E do not permit a decision between (II) and (III), for in the absence of reference substances definitely known to contain the NHg_2 grouping it is not possible to estimate $-\Delta H$ or E corresponding to Rammelsberg's formula. However, the data for the loss of weight on heating correspond definitely to the reaction $HgO,HgCl_2,2NH_3 \longrightarrow HgO,HgCl_2,NH_3 + NH_3$ rather than to $3Hg{\cdot}NH_2Cl \longrightarrow NHg_2Cl + HgCl_2 + NH_3$ or to $NHg_2Cl,NH_4Cl \longrightarrow NHg_2Cl + NH_3 + HCl$, and so again support (III). Finally, the fact that there is no change in the content of " basic " mercury is strong confirmation of Britton and Wilson's formula (III).

Experimental

Preparation of Materials.—Diamminomercuric iodide. This was prepared by Saha and Choudhury's method (*Z. anorg. Chem.*, 1912, **77**, 44) (Found : Hg, 41·14, 41·22; I, 52·24, 52·08; NH_3, 6·84, 6·91. Calc. for $HgI_2,2NH_3$: Hg, 41·07; I, 51·96; NH_3, 6·97%).

Dipyridinomercuric chloride. Mercuric chloride (50 g.) was warmed with redistilled pyridine (100 ml.) until complete solution was obtained. On cooling, white crystals formed which were filtered off, washed with a little pyridine, and rapidly dried with filter-paper. The product was stored on porous tile in a desiccator (freshly calcined CaO); m. p. 108° (rapid heating) (Schroeder, *Z. anorg. Chem.*, 1905, **44**, 11, gives 103°; Ströholm, *ibid.*, 1908, **57**, 106, gives 108°). Analysis (Found : Hg, 47·7, 47·8; Cl, 16·9, 16·8; C_5H_5N, 35·0, 35·15%; Hg : Cl =

1 : 1·997. Calc. for $HgCl_2$,1·88C_5H_5N : Hg, 47·8; Cl, 17·0; C_5H_5N, 35·4%) showed some decomposition.

Fusible white precipitate. 200 C.c. of a solution of 4·5N-ammonia containing 30 g. of ammonium chloride were heated to boiling, and a solution of mercuric chloride (50 g./l.) was added dropwise, with stirring, until the precipitate first formed after the addition of each drop just did not dissolve on stirring. The whole was then cooled, and the crystals were filtered off, washed with acetone, and dried at room temperature in a desiccator (Found : Hg, 65·4; Cl, 23·3, 23·5; NH_3, 11·2, 11·05. Calc. for $HgCl_2.2NH_3$: Hg, 65·6; Cl, 23·1; NH_3, 11·15%).

Infusible white precipitate. The method of B.P., 1914, was adopted (Found : Hg, 77·1, 77·2; Cl, 13·4, 13·2; NH_3, 6·7, 6·7. Calc. for NH_2·HgCl: Hg, 79·6; Cl, 14·1; N, expressed as NH_3, 6·75%. Calc. for $HgO,HgCl_2.2NH_3$: Hg, 76·8; Cl, 13·6; NH_3, 6·5%).

Our thanks are offered to Professor H. T. S. Britton for bringing this problem to our attention and for his constant encouragement. One of us (D. R. G.) acknowledges the receipt of a maintenance grant from the Department of Scientific and Industrial Research, and a College Research Scholarship.

UNIVERSITY COLLEGE, EXETER. [*Received, November 20th*, 1952.]

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305. *Aminophenoxazines as Possible Antitubercular Agents. Part I. A New Method for the Synthesis of 3-Aminophenoxazine.*

By B. BOOTHROYD and EDWARD R. CLARK.

Desulphonation of 3-nitrophenoxazine-1-sulphonic acid (IV; R = SO_3H) and decarboxylation of 3-nitrophenoxazine-1-carboxylic acid (IV; R = CO_2H) have been unsuccessfully attempted as possible routes to 3-aminophenoxazine (I; R = H). Partial reduction of 1 : 3-dinitrophenoxazine (IV; R = NO_2) with sodium hydrogen sulphide yields a complex phenolic substance.

10-Benzyl-3-nitrophenoxazine (V; R = CH_2Ph, R′ = H) and its 8-chloro-analogue (R′ = Cl) have been synthesized and reduced catalytically. The former yields the corresponding amine and finally 3-aminophenoxazine. Partial removal of the chlorine atom accompanies the debenzylation of the 8-chloro-analogue.

THE report by Clapp, Clark, English, Fellows, Grotz, and Shepherd (*J. Amer. Chem. Soc.*, 1952, **74**, 1989) on the possible use of phenoxazine derivatives as antitubercular agents prompts the authors to record similar investigations conducted during the last 3 years.

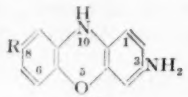
The earliest record of the antitubercular activity of phenoxazine derivatives is de Witt's finding (*J. Inf. Dis.*, 1913, **13**, 378) that New Methylene Blue G.G. stained the tubercle bacillus *in vitro* and penetrated the tubercle *in vivo*. de Witt did not, however, follow this up and phenoxazines, as antitubercular agents, were apparently neglected until the much more recent publications by Okomoto (*Japan. Med. J.*, 1948, **1**, 422; *Chem. Abs.*, 1951, **45**, 5757), Crossley *et al.* (*J. Amer. Chem. Soc.*, 1952, **74**, 573, 578, 584) and Clapp *et al.* (*loc. cit.*).

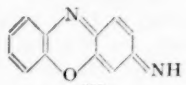
A number of analogous ring structures and other substances bearing a superficial resemblance to phenoxazine have however been investigated. Thus Freedlander (*Proc. Soc. Exp. Biol. N.Y.*, 1944, **57**, 106) suggested that the antitubercular activity of phenothiazine was due to its oxidation to the 3-quinone. The presence of the quinonoid structure could also be the basis of activity in certain phenazines, *e.g.*, anilinoaposafranine (Barry, Belton, Conalty, and Twomey, *Nature*, 1948, **162**, 622), induline (Kudryavtsev, *Compt. rend. Acad. Sci. U.R.S.S.*, 1941, **33**, 292; *Chem. Abs.*, 1944, **38**, 5878), and 2 : 3-diaminophenazine (Erlenmeyer, Noll, and Sorkin, *Helv. Chim. Acta*, 1949, **32**, 605).

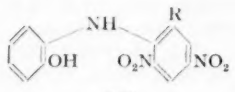
The occurrence of antitubercular activity in these compounds and in various amino-substituted diphenyl ethers (Barry, O'Rourke, and Twomey, *Nature*, 1947, **160**, 800) encouraged the belief that simple aminophenoxazines, capable of oxidation to *o*- or *p*-quinones, would also be active. Further, if the ability to penetrate the tubercle, *in vivo*,

was inherent in the phenoxazine structure then the envisaged substances would be able to concentrate at the site of infection in the animal.

We have therefore attempted to synthesize 3-amino- (I; R = H) and 3-amino-8-chlorophenoxazine (I; R = Cl) for biological testing. [Barry, O'Rourke, and Twomey (*loc. cit.*) found that substitution by chlorine greatly increased the antitubercular activity of 4-aminodiphenyl ethers.]


(I)

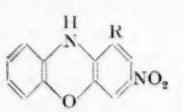

(II)

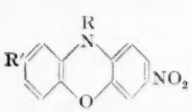

(III)

The chloroplatinate of phenoxazim (II) has been prepared (Kehrmann and Grely, *Ber.*, 1909, **42**, 348) from 3 : 7-dinitrophenoxazine, obtained by the direct nitration of phenoxazine. Neither the base nor its salts were apparently obtained pure. This method is not suitable for the synthesis of 3-amino-8-chlorophenoxazine.

The production of 3-nitrophenoxazine (IV; R = H) by heating 2′-hydroxy-2 : 4-dinitrodiphenylamine (III; R = H) with anhydrous sodium acetate in glycerol has been claimed by Kehrmann and Ramm (*Ber.*, 1920, **53**, 2265), but refuted by Brady and Wallace (*J.*, 1930, 1218). The dark brown colour and m. p. (>300°) ascribed to 3-nitrophenoxazine by Kehrmann and Ramm are not consistent with the known properties of well-authenticated nitrophenoxazines: other nitrophenoxazines are well-defined red or violet crystalline compounds with sharp melting points around 200° [*e.g.*, (IV; R = Me) forms red needles, m. p. 212—213° (decomp.) (Boothroyd and Clark, following paper)].

Substitution in the 6-position in the diphenylamine is known to facilitate ring closure; the possibility of removing this group, after ring closure, was therefore investigated. The first synthesis attempted was the desulphonation of 3-nitrophenoxazine-1-sulphonic acid (IV; R = SO_3H). However, hydrochloric or sulphuric acid gave unidentified decomposition products. Acid hydrolysis of 3-aminophenoxazine-1-sulphonic acid, prepared by reduction with tin and hydrochloric acid, gave no better result, though the somewhat similar 4 : 4′-diaminodiphenylamine-2-sulphonic acid has been successfully desulphonated (U.S.P. 2,022,889). Decarboxylation of the corresponding carboxylic acid (IV; R = CO_2H), by heating it with (*a*) glycerol at 250°, (*b*) soda-lime at 265°, or (*c*) quinoline and copper powder, was similarly unsuccessful. [2-Chloro-3 : 5-dinitrobenzoic acid, required for the synthesis of (IV; R = CO_2H), was readily obtained from 3 : 5-dinitrosalicylic acid, phosphorus oxychloride, and diethylaniline; this is a more convenient method than the nitration of *o*-chlorobenzoic acid.] Preferential reduction of the 1-nitro-group of the readily accessible (IV; R = NO_2) (Turpin, *J.*, 1891, **59**, 714), followed by diazotization and reductive decomposition, should give the desired 3-nitrophenoxazine. Treatment of (IV; R = NO_2) with sodium hydrogen sulphide solution yielded a green crystalline product (probably phenolic), having a bright metallic lustre. Digestion with dilute sodium hydroxide solution followed by acidification yielded a greenish-brown product, m. p. 201—203° (decomp.), of empirical formula $C_{26}H_{24}O_9N_6$. Two acidic groupings in a molecule of molecular weight *ca.* 290 were shown by potentiometric titration; the absence of amino-groups was indicated by inability to form a diazo-compound. Further work will be necessary to elucidate the structure of this product.

(IV) 

 (V)

Ring closure of diphenylamines (as III; R = H) is facilitated by substitution of the amino-hydrogen atom; thus, Roberts and Clark (*J.*, 1935, 1312) converted 2′-hydroxy-*N*-methyl-2 : 4-dinitrodiphenylamine into 10-methyl-3-nitrophenoxazine (V; R = Me, R′ = H).

10-Benzyl-3-nitrophenoxazine (V; R = CH_2Ph, R′ = H) has now been similarly

prepared. Its catalytic reduction yielded 3-aminophenoxazine (I; R = H), reduction of the nitro-group being followed by fission of the *N*-benzyl linkage. In practice, *N*-benzyl-2′-hydroxy-2 : 4-dinitrodiphenylamine, prepared by the condensation of 1-chloro-2 : 4-dinitrobenzene and *o*-benzylaminophenol, was converted into the corresponding phenoxazine without being isolated. The *o*-benzylaminophenol was obtained in excellent yield by the reduction of the corresponding Schiff's base with lithium aluminium hydride; this was in marked contrast to the poor yields obtained by using magnesium and methyl alcohol (18—24% of theory) or by catalytic hydrogenation with Raney nickel as catalyst (20—25% of theory). *N*-Benzyl-5-chloro-2-hydroxyaniline, used to prepare 10-benzyl-8-chloro-3-nitrophenoxazine (V; R = CH_2Ph, R′ = Cl), was obtained similarly.

Reduction of 10-benzyl-3-nitrophenoxazine by using platinum oxide, acetic acid, and hydrogen at 5 atmospheres gave an almost theoretical yield of the 10-benzyl-3-amino-compound. Similarly, palladous oxide in alcohol with hydrogen at atmospheric temperature and pressure, did not promote debenzylation, though the colourless solution obtained rapidly became red in air, owing presumably to oxidation of a small amount of 3-aminophenoxazine to phenoxazim. In acetic acid debenzylation could be induced by raising the temperature to 90°, after the reduction of the nitro-group. Even then, however, only 27% of phenoxazim hydrochloride was isolated, while 48% of 3-amino-10-benzylphenoxazine was obtained. Recrystallization of the phenoxazim hydrochloride was not possible; it was identified as the picrate.

3-Aminophenoxazine (I; R = H) was obtained by using palladium chloride–charcoal in *n*-butyl alcohol. Again the nitro-group was reduced at room temperature, and the solution then heated to 90° to induce removal of the benzyl group. Solutions of the free base in dilute hydrochloric acid rapidly darkened in air owing to oxidation to phenoxazim.

The use of acetic acid in place of *n*-butyl alcohol gave good yields of the monoacetyl derivative of 3-aminophenoxazine, identical with that obtained by acetylation of the free base. The acetyl derivative was insoluble in both hot and cold dilute hydrochloric acid, but in air hydrolysis and oxidation gave a solution of phenoxazim hydrochloride.

Hydrogenation of 10-benzyl-8-chloro-3-nitrophenoxazine in acetic acid solution with palladium chloride—charcoal yielded a mixture, and some dechlorination accompanied debenzylation. The mixture was readily oxidized by air, and the constituents could not be separated by fractional crystallization of the amines or of the picrates formed from the oxidized mixture.

In a preliminary examination, *in vitro*, of 3-aminophenoxazine hydrochloride against *M. tuberculosis* (H37Rv), inhibition of growth was observed down to a dilution of 1 in 1×10^7. Experiments *in vivo* are in progress and details will be published elsewhere.

Experimental

Some analyses are by Mrs. Richards.

Effect of Acid on 3-Nitrophenoxazine-1-sulphonic Acid.—When potassium 3-nitrophenoxazine-1-sulphonate (Ullmann and Herre, *Annalen*, 1909, **366**, 112) was heated with 8N-hydrochloric acid for 5 hr. or with 50% sulphuric acid for 7 hr., much decomposition occurred; in the former experiment a small amount of the S-*benzylthiuronium* salt was obtained, identical with an authentic specimen, m. p. 213—214° (Found: C, 50·75; H, 3·7; N, 11·3; S, 13·45. $C_{20}H_{18}O_6N_4S_2$ requires C, 50·6; H, 3·8; N, 11·8; S, 13·5%).

3-Aminophenoxazine-1-sulphonic Acid.—Granulated tin (3 g.) was slowly added to a stirred refluxing suspension of potassium 3-nitrophenoxazine-1-sulphonate (5 g.) in *ca.* 7N-hydrochloric acid (200 c.c.), and stirring was continued until the mixture was colourless. The insoluble product was recrystallized from water (800 c.c.) containing a small amount of sodium hydrosulphite (dithionite), giving grey needles (2·9 g.), which became red in air (Found: C, 51·5; H, 3·2. Calc. for $C_{12}H_{10}O_4N_2S$: C, 51·7; H, 3·6%). With hot hydrochloric acid only a black solid, insoluble in acid and alkali, was obtained.

2-Chloro-3 : 5-dinitrobenzoic Acid.—Diethylaniline (50 c.c.) was slowly added to a solution of 3 : 5-dinitrosalicylic acid (25 g.) in phosphorus oxychloride (200 c.c.), with cooling. The solution, protected from atmospheric moisture, was heated under reflux for 2 hr. After cooling, the mixture was poured on crushed ice (2 kg.), and the crude product dried and extracted with

hot 50% aqueous ethanol (100 c.c.), leaving a small insoluble residue. The extract, on cooling, first deposited an oil and then a crystalline precipitate, which, on recrystallization from 50% aqueous ethanol, yielded 2-chloro-3 : 5-dinitrobenzoic acid (19·8 g.), m. p. 198—199° (Purgotti and Contardi, *Gazzetta*, 1901, **31**, 527, record m. p. 199°).

3-Nitrophenoxazine-1-carboxylic Acid.—Prepared according to Ullmann's method (*Annalen*, 1909, **366**, 90), this formed red needles, m. p. 292—292·5° (decomp.) (Found: C, 57·2; H, 2·8; N, 9·85. Calc. for $C_{13}H_8O_5N_2$: C, 57·35; H, 2·9; N, 10·3%).

Reduction of 1 : 3-*Dinitrophenoxazine by using Sodium Hydrogen Sulphide.*—Methyl alcohol (225 c.c.) was added to a solution of hydrated sodium sulphide (21 g.) and sodium hydrogen carbonate (21 g.) in water (150 c.c.), and after 15 min. the precipitate was filtered off. This solution of sodium hydrogen sulphide was added during 1½ hr. to a stirred, refluxing mixture of 1 : 3-dinitrophenoxazine (8·4 g.) (Turpin, *loc. cit.*) and methyl alcohol (200 c.c.). The dark brown solution was heated under reflux for a further 15 min. and then left overnight in the ice-box. The mass of green needles (6·2 g.) was washed with 50% aqueous methyl alcohol. Digestion of this green product (0·5 g.) for 1 hr. with hot *ca.* 2N-sodium hydroxide (10 c.c.), neutralization (litmus) of the solution with dilute hydrochloric acid, and crystallization of the *product* (0·45 g.) from 50% aqueous ethanol yielded greenish-brown needles, m. p. 201—203° (decomp.) (Found: C, 55·3; H, 4·3; N, 15·0. $C_{26}H_{24}O_9N_6$ requires C, 55·3; H, 4·25; N, 14·9%).

o-*Benzylaminophenol.*—(*a*) Magnesium turnings were added to a solution of *o*-benzylideneaminophenol (15 g.) (Pictet and Ankersmit, *Annalen*, 1891, **266**, 140) in methyl alcohol. The stirred mixture was warmed gently on a steam-bath for about an hr. in all, the reaction being controlled by use of a cold-water bath when necessary. The excess of methyl alcohol was distilled off and the residue decomposed with ice–water (100 c.c.) and acetic acid (60 c.c.). The black sticky product was dissolved in benzene, the aqueous liquor extracted with benzene (3 × 75 c.c.), and the combined benzene solutions were dried (Na_2SO_4).

Three methods were used for working up the resulting benzene solution: (i) Distillation yielded o-*benzylaminophenol*, b. p. 135—155°/0·1 mm., which crystallized from *cyclo*hexane or ligroin (b. p. 60—80°) in pale brown plates (4·2 g.), m. p. 88—89° (Found: C, 78·45; H, 6·3; N, 7·0. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·5; N, 7·0%). (ii) The benzene solution was extracted with dilute hydrochloric acid (3 × 75 c.c.), the extract neutralized with sodium hydrogen carbonate, and the precipitate dried and extracted with ligroin (b. p. 60—80°). Concentration of the ligroin solution gave the required *o*-benzylaminophenol (2·7 g.), m. p. 88—89°. (iii) The precipitate obtained in (ii) was distilled (b. p. 140—155°/0·1 mm.), and the distillate recrystallized from *cyclo*hexane, yielding *o*-benzylaminophenol, m. p. 88—89°.

(*b*) A mixture of *o*-aminophenol (11 g.) and benzaldehyde (12·7 g.) in ethanol (100 c.c.) was reduced at 70° by using Raney nickel (1·2 g.) as catalyst and an initial hydrogen pressure of 70 atm. The uptake of hydrogen was only *ca.* 75% of that calculated. The catalyst was filtered off, the alcohol evaporated, the residue distilled, and the *o*-benzylaminophenol (5·1 g.) recrystallized from ligroin (b. p. 60—80°).

(*c*) Reduction of *o*-benzylideneaminophenol (6·5 g.) under the conditions described in (*b*) yielded only 1·4 g. of the required product.

(*d*) *o*-Benzylideneaminophenol (6·9 g.), in dry ether (125 c.c.), was during 20 min. added to a stirred suspension of lithium aluminium hydride (0·9 g.) in dry ether (75 c.c.) so that gentle refluxing took place. The mixture was then heated on a steam-bath for 1 hr., water added to destroy the excess of lithium aluminium hydride, and the mixture acidified with dilute sulphuric acid. The ethereal layer was extracted further with dilute sulphuric acid, the combined acid extracts were neutralized (sodium hydrogen carbonate), and the precipitate was dried. Extraction (Soxhlet) of this solid with ether, evaporation of the resulting solution, and recrystallization from *cyclo*hexane yielded *o*-benzylaminophenol (6·3 g.), m. p. 89—90° (mixed m. p. with an authentic specimen 88—89°).

N-*Benzylidene-5-chloro-2-hydroxyaniline.*—5-Chloro-2-hydroxyaniline (14·8 g.) (Mottier, *Arch. Sci. Phy. Nat.*, 1934, **16**, 301; *Chem. Abs.*, 1935, **29**, 3322) was mixed with freshly distilled benzaldehyde (10·1 c.c.); an immediate reaction yielded a fawn-coloured solid. Recrystallization from 60% aqueous alcohol yielded long rectangular orange-brown plates of N-*benzylidene-5-chloro-2-hydroxyaniline* (20·5 g.), m. p. 93·5—94° (Found: C, 66·9; H, 4·0; N, 6·1; Cl, 15·4. $C_{13}H_{10}ONCl$ requires C, 67·4; H, 4·3; N, 6·0; Cl, 15·3%).

N-*Benzyl-5-chloro-2-hydroxyaniline.*—*N*-Benzylidene-5-chloro-2-hydroxyaniline (5·7 g.) was reduced by using lithium aluminium hydride (0·58 g.) as described above. Just sufficient dilute sulphuric acid was added to dissolve the thick yellow precipitate which formed on the addition

of water to the reaction mixture. The yellow ethereal layer was separated and evaporated to dryness. Recrystallization of the residue from *cyclo*hexane yielded plates of *N-benzyl-5-chloro-2-hydroxyaniline* (4·9 g.), m. p. 119—120° (Found: C, 67·2; H, 5·1; N, 6·0; Cl, 14·85. $C_{13}H_{12}ONCl$ requires C, 66·8; H, 5·1; N, 6·0; Cl, 15·2%).

10-Benzyl-3-nitrophenoxazine.—A solution of sodium hydroxide (4 g.) in 50% aqueous alcohol (60 c.c.) was slowly added to a stirred, refluxing solution of *o*-benzylaminophenol (8·5 g.) and 1-chloro-2 : 4-dinitrobenzene (9 g.) in alcohol (85 c.c.). The mixture was heated for a further 1 hr. and then left in the ice-box overnight. The bright red crystals were filtered off, and washed with dilute sodium hydroxide solution and with alcohol. Recrystallization from acetone gave red needles of *10-benzyl-3-nitrophenoxazine* (11·3 g.), m. p. 175—175·5° (Found: C, 71·9; H, 4·2; N, 8·6. $C_{19}H_{14}O_3N_2$ requires C, 71·7; H, 4·4; N, 8·8%).

10-Benzyl-8-chloro-3-nitrophenoxazine.—Condensation of *N*-benzyl-4-chloro-2-aminophenol (2·5 g.) and 1-chloro-2 : 4-dinitrobenzene (2·5 g.), by using sodium hydroxide (1·2 g.) as described above, gave *10-benzyl-8-chloro-3-nitrophenoxazine* (2·6 g.), orange-red needles (from benzene), m. p. 226·5—227° (Found: C, 64·9; H, 3·8; N, 8·3; Cl, 10·3. $C_{19}H_{13}O_3N_2Cl$ requires C, 64·7; H, 3·7; N, 8·0; Cl, 10·1%).

Reduction of 10-Benzyl-3-nitrophenoxazine.—(*a*) 10-Benzyl-3-nitrophenoxazine (1·6 g.) in acetic acid (50 c.c.) was reduced, by using platinum oxide (0·1 g.) and hydrogen at atmospheric pressure. Absorption ceased when sufficient hydrogen to reduce the nitro-group had been taken up. After filtration under nitrogen, the acetic acid solution was made alkaline with 40% aqueous sodium hydroxide. Recrystallization of the precipitate from 1 : 1-glacial acetic acid–2% sodium dithionite solution yielded greenish-grey diamond-shaped plates of *3-amino-10-benzylphenoxazine monohydrate*, m. p. 188—189° (1·5 g.) (Found: C, 74·6; H, 5·9; N, 9·5. $C_{19}H_{16}ON_2,H_2O$ requires C, 74·5; H, 5·9; N, 9·15%). Repetition of the experiment at 90° gave a similar result.

(*b*) 10-Benzyl-3-nitrophenoxazine (2·5 g.) in alcohol (75 c.c.) was reduced, at atmospheric pressure and temperature, by using palladous oxide as catalyst. Uptake of hydrogen ceased when 700 c.c. of the required 830 c.c. had been absorbed. The filtered solution was concentrated to 25 c.c. under nitrogen; addition of water (75 c.c.) precipitated a tar which was taken into benzene. This solution was dried (Na_2SO_4) and the amine hydrochlorides precipitated by dry hydrogen chloride. Extraction with water then yielded a red solution of phenoxazim hydrochloride, a very small amount of which could be isolated by neutralization, extraction with benzene, and precipitation with hydrogen chloride. The water-insoluble hydrochloride, on trituration with benzene, yielded a blue powder (1·7 g.), m. p. 213—215° (decomp.).

Treatment with sodium carbonate solution, extraction with benzene, evaporation of the green benzene solution, and recrystallization of the residue from 50% aqueous acetic acid containing a little sodium dithionite, yielded small green-grey crystals, m. p. 188—189°; m. p. of mixture with 3-amino-10-benzylphenoxazine monohydrate, 188—189°.

(*c*) 10-Benzyl-3-nitrophenoxazine (5·6 g.) was reduced in acetic acid (50 c.c.) by using palladous oxide (1 g.). 1790 c.c. of hydrogen were absorbed initially and then, on heating to 90°, a further 220 c.c. (calc. vol. required, 2215 c.c.). Air was drawn through the filtered solution to oxidize the amines and, after addition of an equal volume of water, the acid was neutralized with ammonia (*d* 0·88). Extraction with benzene yielded a greenish-brown solution which was dried and then concentrated to 150 c.c. under reduced pressure. Passage of dry hydrogen chloride precipitated a mixture of amine hydrochlorides, extraction of which, with dilute hydrochloric acid, gave a red solution and left crude 3-amino-10-benzylphenoxazine hydrochloride (2·8 g.).

The red acid solution was made alkaline and extracted with benzene, the benzene solution dried (Na_2SO_4), and the hydrochloride precipitated as before yielding phenoxazim hydrochloride (1·1 g.). Attempts to prepare the phenylurea and the acetyl derivative were unsucessful. It was characterized as *phenoxazim picrate*, which, after recrystallization from *ca.* 0·75% aqueous picric acid solution, had m. p. 186—187° (decomp.) (Found: C, 50·8; H, 2·7; N, 16·3. $C_{18}H_{11}O_8N_5$ requires C, 50·8; H, 2·6; N, 16·5%).

Carrying out the entire reduction at 90° gave decomposition products and smaller amounts of the two amines.

(*d*) 10-Benzyl-3-nitrophenoxazine (2·2 g.) was reduced in *n*-butyl alcohol (50 c.c.) with 10% palladium chloride–charcoal (1 g.) as catalyst. The volume of hydrogen for the reduction of the nitro-group was smoothly absorbed and, at 90°, rapid debenzylation occurred. The cooled solution was filtered under nitrogen, concentrated under reduced pressure (nitrogen) to *ca.* 5 c.c., and then left in the ice-chest. The solid product was recrystallized from a 1 : 3-alcohol–2%

aqueous dithionite solution, yielding pale fawn-coloured plates of 3-*aminophenoxazine* (0·75 g.), m. p. 172—173° (decomp.) (Found: C, 72·9; H, 4·8; N, 14·35. $C_{12}H_{10}ON_2$ requires C, 72·7; H, 5·05; N, 14·1%). The monoacetyl derivative had m. p. and mixed m. p. 171·5—172·5° (decomp.).

(*e*) Replacement of the *n*-butyl alcohol in (*d*) by acetic acid resulted in the production of 3-*acetamidophenoxazine* (1·1 g.), m. p. 171·5—172·5° (decomp.) (Found: C, 70·2; H, 5·25; N, 11·7. $C_{14}H_{12}O_2N_2$ requires C, 70·0; H, 5·0; N, 11·7%).

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306. *Aminophenoxazines as Possible Antitubercular Agents. Part II.**

By B. BOOTHROYD and EDWARD R. CLARK.

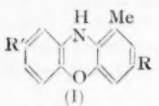
A number of 1-amino- and 3-amino-phenoxazines have been synthesised, including 3-amino-8-chloro-1-methylphenoxazine (I; R = NH_2, R′ = Cl), 1-amino-8-chlorophenoxazine (II; R = H, R′ = Cl), 3-aminophenoxazine-1-carboxylic acid (III), 3-amino-1-methylphenoxazine (I; R = NH_2, R′ = H), and 1 : 3-diaminophenoxazine (II; R = NH_2, R′ = H).

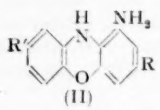
The reaction between 1-chloro-2 : 4 : 5-trinitrobenzene and *o*-benzylaminophenol yields a mixture of 10-benzyl-2-chloro-3-nitro- and 10-benzyl-2 : 3-dinitro-phenoxazine; catalytic reduction of the latter failed to yield any identifiable product.

While some of the compounds have shown marked tuberculostatic activity *in vitro*, no influence on the course of tubercular infection in guinea pigs has been observed.

3-AMINO-1-METHYLPHENOXAZINE (I; R = NH_2, R′ = H) and its 8-chloro-analogue (I; R = NH_2, R′ = Cl) have been prepared in order to determine the influence of the halogen substituent on antitubercular activity.

The 2-chloro-3 : 5-dinitrotoluene needed was obtained from phosphorus oxychloride, diethylaniline, and 2-hydroxy-3 : 5-dinitrotoluene, this method giving a better yield than Ullmann and Sane's toluene-*p*-sulphonyl chloride method (*Ber.*, 1911, **44**, 3735). 1-Methyl-3-nitrophenoxazine (I; R = NO_2, R′ = H) was prepared by Ullmann and Sane (*loc. cit.*) by condensation of 2-chloro-3 : 5-dinitrotoluene with *o*-aminophenol and cyclisation of the purified 2′-hydroxy-6-methyl-2 : 4-dinitrodiphenylamine by using dilute alcoholic sodium hydroxide. Considerably improved yields are obtained when the intermediate diphenylamine is not isolated before cyclisation. The 8-chloro-analogue (I; R = NO_2, R′ = Cl) was prepared in one operation by use of aqueous alcoholic sodium hydroxide on 2-amino-4-chlorophenol and 2-chloro-3 : 5-dinitrotoluene.


(I)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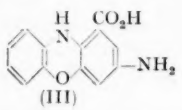
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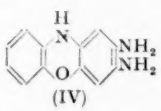
(IV)

The corresponding aminophenoxazines were obtained by catalytic reduction by using Adams's platinum oxide and acetic acid. This was preferred to the use of stannous chloride or tin and hydrochloric acid which give the tin complexes from which it is difficult to isolate the free bases. The bases were isolated in their oxidised forms as hydrochlorides; recrystallisation of these was not possible and attempts to purify them by reprecipitation failed to remove a very small amount of water-insoluble material. It appears that a little of the free base is precipitated with the hydrochloride.

1-Amino- (II; R = R′ = H) and 1-amino-8-chloro-phenoxazine (II; R = H, R′ = Cl) were then prepared; these compounds can be oxidised to *ortho*-quinones. 1-Nitrophenoxazine has been prepared by Ullmann (*Annalen*, 1909, **366**, 110) and its reduction, by

* Part I, preceding paper.

using stannous chloride and hydrochloric acid, was reported by Kehrmann and Lowry (*Ber.*, 1911, **44**, 3006). The hydrochloride, and that of the 8-chloro-analogue have been obtained. The former was rather insoluble in water as also was the oxidised form. 1-Aminophenoxazine-3-carboxylic acid (II; R = CO_2H, R′ = H) was therefore synthesised, since it could be tested as its sodium salt.

The preparation of 1-nitrophenoxazine-3-carboxylic acid has been claimed by Ullmann (*Annalen*, 1909, **366**, 96) but neither melting point nor analytical data were given. By using a similar method, an analytically pure sample has been obtained. Reduction of the nitro-carboxylic acid by using stannous chloride gave a highly insoluble product, recrystallisation of which yielded what was apparently a mixture of the hydrochloride and the free amino-acid.

3-Aminophenoxazine-1-carboxylic acid (III) was synthesised by reduction of the corresponding nitro-compound with stannous chloride in hydrochloric acid. Recrystallisation from 50% hydrochloric acid yielded the hydrochloride monohydrate.

1 : 3-Diamino- (II; R = NH_2, R′ = H) and 2 : 3-diamino-phenoxazine (IV) are of interest, the former, since it is capable of conversion into both *ortho*- and *para*-quinonoid structures and, the latter, since it bears a close resemblance to the tuberculostatic 2 : 3-diaminophenazine (Erlenmeyer, *Helv. Chim. Acta*, 1949, **32**, 605). 1 : 3-Dinitrophenoxazine was reduced by Kehrmann (*Ber.*, 1899, **32**, 2603) by using stannous chloride in hydrochloric acid. Catalytic reduction in acetic acid solution with platinum oxide proceeded smoothly, and is to be preferred. The product was characterised as the sulphate and by oxidation to the imine from which the picrate was formed.

Owing to the absence of any $C_{(1)}$-substituent, the synthesis of 2 : 3-diaminophenoxazine was approached along similar lines to those used for 3-aminophenoxazine (see Part I).

According to Nietzki and Zänker (*Ber.*, 1903, **36**, 3953) 5-chloro-2 : 4-dinitroaniline can be obtained by the action of ammonia on 1-chloro-2 : 4 : 5-trinitrobenzene, giving rhombic plates, m. p. 174—176°, or on 1 : 3-dichloro-4 : 6-dinitrobenzene, giving long needles, m. p. 182°. No experimental details are given. When 1-chloro-2 : 4 : 5-trinitrobenzene and ammonia reacted in alcoholic solution in the presence of a little sodium carbonate, 5-chloro-2 : 4-dinitroaniline, m. p. 184·5—185° and some 1 : 3-diamino-4 : 6-dinitrobenzene were obtained, the former being identified as the acetanilide (Kehrmann and Stanoyevitch, *Helv. Chim. Acta*, 1925, **8**, 664). Recrystallisation of the aniline from benzene–ligroin gave a product, m. p. 176—176·5°. Five crystallisations of this form from 50% aqueous alcohol raised the m. p. to 184—185°; a mixture of approximately equal parts of the two forms melted at 181—182°.

The use of dry benzene as solvent in the preparation of the aniline caused a marked improvement in the yield. Samples obtained by both methods gave high analytical results for carbon, due presumably to excessive formation of nitrous fumes on combustion.

Kehrmann and Stanoyevitch (*loc. cit.*) obtained 5-acetamido-2 : 4-dinitrodiphenylamine from 5-chloro-2 : 4-dinitroacetanilide and aniline. By using *o*-aminophenol, in place of aniline, and sodium acetate in aqueous ethanol as the condensing agent, only a dark tar was obtained. Only 5-chloro-2 : 4-dinitroaniline was identified in the products of the attempted cyclisation of this material.

The reaction between 1-chloro-2 : 4 : 5-trinitrobenzene and *o*-benzylaminophenol yielded 10-benzyl-2 : 3-dinitro- and 10-benzyl-2-chloro-3-nitro-phenoxazine. The production of the former is remarkable, but the ratio of the dinitrophenoxazine to the chloronitrophenoxazine, approximately 3 : 1, is even more so. No conclusions can be drawn from this result, however, as only 26% of the starting materials was accounted for.

Preliminary biological tests have been carried out. 3-Imino-1-methylphenoxazine hydrochloride and its 8-chloro-analogue inhibited the growth, *in vitro*, of *M. tuberculosis* (H37Rv) at dilutions of 1 in 100,000, while 1-aminophenoxazine hydrochloride inhibited growth at dilutions down to 10^9.

Despite the poor analytical figures obtained for the product of reduction of 1-nitrophenoxazine-3-carboxylic acid, it was believed to be the required amino-acid, probably, as stated above, as a mixture of hydrochloride and free amino-acid. It was therefore neutralised with sodium carbonate solution and the resulting sodium salt tested; no

inhibition of the growth of *M. tuberculosis* was observed, even at concentrations of 1 in 1000.

Administration of 3-imino-1-methylphenoxazine hydrochloride, its 8-chloro-analogue, and 1-aminophenoxazine hydrochloride to infected guinea pigs during 40 days had little influence on the course of the tubercular infection. Further biological tests are in progress. The results of these and full details of the above biological examinations will be published elsewhere.

Experimental

Some of the analyses are by Mrs. Richards.

2-Chloro-3 : 5-dinitrotoluene.—Diethylaniline (60 c.c.) was added, with cooling, to a solution of 2-hydroxy-3 : 5-dinitrotoluene (40 g.) in phosphorus oxychloride (235 c.c.), which was then heated on the steam-bath for 2 hr., allowed to cool, and carefully poured on crushed ice (1·5 kg.). 2-Chloro-3 : 5-dinitrotoluene (37·9 g.) was recrystallised from alcohol, yielding pale yellow plates, m. p. 63—64°.

1-Methyl-3-nitrophenoxazine.—A solution of *o*-aminophenol (11 g.) and 2-chloro-3 : 5-dinitrotoluene (21·6 g.) in *ca.* 2N-sodium acetate (60 c.c.) and ethyl alcohol (100 c.c.) was stirred and heated under reflux for 5 hr. *ca.* 2N-Sodium hydroxide solution (75 c.c.) was slowly added and the red solution boiled for 30 min. and then set aside overnight in the ice-box. The dark brown product was washed with dilute sodium hydroxide and a little ethanol, and then recrystallised from toluene, yielding 1-methyl-3-nitrophenoxazine (18·9 g.), m. p. 212—213° (decomp.) (Found: C, 64·5; H, 4·2; N, 11·3. Calc. for $C_{13}H_{10}O_3N_2$: C, 64·4; H, 4·1; N, 11·6%).

8-Chloro-1-methyl-3-nitrophenoxazine.—To a refluxing solution of 2-amino-4-chlorophenol (3·6 g.) and 2-chloro-3 : 5-dinitrotoluene (5·4 g.) in ethyl alcohol (30 c.c.), *ca.* 2N-sodium hydroxide (25 c.c.) was added slowly, with stirring. The mixture was heated on the steam-bath and stirred for a further 2 hr., set aside overnight in the ice-box and then filtered, yielding a slightly sticky solid which was washed with dilute sodium hydroxide and alcohol. *8-Chloro-1-methyl-3-nitrophenoxazine* formed red needles (5·0 g.), m. p. 272—273° (decomp.) (from nitrobenzene or chlorobenzene) (Found: C, 56·6; H, 3·2; N, 10·4; Cl, 13·15. $C_{13}H_9O_3N_2Cl$ requires C, 56·4; H, 3·3; N, 10·1; Cl, 12·85%).

3-Imino-1-methylphenoxazine.—1-Methyl-3-nitrophenoxazine (2·7 g.) in suspension in glacial acetic acid (50 c.c.) was reduced at room temperature by using Adams's platinum oxide (0·1 g.) and an initial hydrogen pressure of 5 atmospheres; the calculated amount of hydrogen was absorbed during 14 hr. The resulting colourless solution, which rapidly became red on exposure to the air, was filtered, concentrated *in vacuo* to 10 c.c., and made alkaline with dilute sodium hydroxide. Dry hydrogen chloride was passed through the dried (Na_2SO_4) benzene solution of the precipitated solid, giving the imine hydrochloride (2·4 g.), which was filtered off, washed with benzene, and dried in a vacuum.

The bulk of the product was very soluble in ethyl alcohol, water, and acetone, but entirely insoluble in benzene, ligroin, and other non-polar solvents.

In an attempt to remove the small amount of water-insoluble material, a filtered aqueous solution of the hydrochloride was made alkaline with sodium hydroxide solution, the imine extracted with benzene, and the hydrochloride precipitated from the dried solution as before. The product again contained a very small amount of water-insoluble material which appeared to be the free base.

Addition of a saturated picric acid solution to a filtered aqueous solution of imine hydrochloride immediately gave a red precipitate. Recrystallisation from a mixture of ethyl alcohol and 30% by volume of saturated aqueous picric acid yielded *3-imino-1-methylphenoxazine picrate*, m. p. >300° (Found: C, 51·9; H, 3·4; N, 16·2. $C_{13}H_{10}ON_2,C_6H_3O_7N_3$ requires C, 51·9; H, 3·0; N, 15·95%).

8-Chloro-3-imino-1-methylphenoxazine.—8-Chloro-1-methyl-3-nitrophenoxazine (2·8 g.) was reduced, and the imine hydrochloride (2·5 g.) isolated as described for the analogue not containing halogen. The *picrate* crystallised from ethanol containing 10% of a saturated aqueous solution of picric acid in long red needles, m. p. >300° (Found: C, 48·5; H, 2·85; N, 14·4. $C_{13}H_9ON_2Cl,C_6H_3O_7N_3$ requires C, 48·15; H, 2·5; N, 14·8%).

1-Chloro-2 : 6-dinitrobenzene.—Prepared from diethylaniline (10·5 c.c.), 2 : 6-dinitrophenol (7 g.), and phosphorus oxychloride (70 c.c.) as described above for 2-chloro-3 : 5-dinitrotoluene, 1-chloro-2 : 6-dinitrobenzene (5·6 g.) had m. p. 86—87° (Ostromisslensky, *J. pr. Chem.*, 1908, **78**, 260, recorded m. p. 87°).

1-*Aminophenoxazine Hydrochloride*.—1-Nitrophenoxazine (0·6 g.) (Ullmann, *Annalen*, 1909, **366**, 110) was reduced with stannous chloride (2·4 g.) and concentrated hydrochloric acid according to Kehrmann and Lowry's method (*Ber.*, 1911, **44**, 3006). To a filtered hot aqueous solution (240 c.c.) of the grey-green crystals (0·6 g.) concentrated hydrochloric acid (240 c.c.) was added; precipitation of the hydrochloride began immediately. Repetition of precipitation next day gave 1-*aminophenoxazine hydrochloride* (0·48 g.), m. p. 249—250° (decomp.) (Found: C, 61·0; H, 4·2; N, 12·3; Cl, 15·6. $C_{12}H_{10}ON_2$,HCl requires C, 61·4; H, 4·7; N, 11·9; Cl, 15·1%).

8-*Chloro*-1-*nitrophenoxazine*.—1-Chloro-2 : 6-dinitrobenzene (2 g.), 2-amino-4-chlorophenol (1·5 g.), ethyl alcohol (15 c.c.), and *ca.* 2N-sodium acetate (10 c.c.) were stirred and heated under reflux for 4 hr. *ca.* 2N-Sodium hydroxide (10 c.c.) was slowly added to the boiling solution and, after a further 30 min.' heating, the mixture was allowed to cool in the ice-box overnight. The mass of fine needles was filtered off, washed with dilute sodium hydroxide solution followed by ethanol, and recrystallised from chlorobenzene; 8-*chloro*-1-*nitrophenoxazine* (1·9 g.) had m. p. 240—241° (decomp.) (Found: C, 54·6; H, 2·6; N, 10·9; Cl, 13·9. $C_{12}H_7O_3N_2Cl$ requires C, 54·85; H, 2·7; N, 10·7; Cl, 13·5%).

1-*Amino*-8-*chlorophenoxazine Hydrochloride*.—8-Chloro-1-nitrophenoxazine (1 g.) was reduced with stannous chloride (3·6 g.) and concentrated hydrochloric acid (15 c.c.) as described for the halogen-free analogue. The crude *hydrochloride* (0·95 g.) was recrystallised from ethyl alcohol—concentrated hydrochloric acid (6 : 4) yielding long rectangular plates, m. p. 228—230° (decomp.) (Found: C, 53·2; H, 4·0; N, 10·5; Cl, 25·9. $C_{12}H_9ON_2Cl$,HCl requires C, 53·5; H, 3·7, N, 10·4; Cl, 26·4%).

1-*Nitrophenoxazine*-3-*carboxylic Acid*.—*o*-Aminophenol (3·3 g.), 4-chloro-3 : 5-dinitrobenzoic acid (7·5 g.), water (30 c.c.), and *ca.* 2N-sodium acetate (15 c.c.) were stirred and heated under reflux for 15 min. To the resulting thick paste was added *ca.* 2N-sodium hydroxide (15 c.c.), and the mixture was stirred and heated for a further 15 min. The dark purple sodium salt was washed with cold brine. More of the sodium salt was obtained by saturating the filtrate and washings with sodium chloride.

An aqueous solution of the combined precipitates was acidified (Congo-red) with dilute hydrochloric acid, the free acid forming a dark gelatinous precipitate. Recrystallisation from 50% aqueous pyridine or acetic acid yielded dark purple needles of 1-*nitrophenoxazine*-3-*carboxylic acid* (6·3 g.), m. p. 320—321° (Found: C, 57·1; H, 3·1; N, 10·4. $C_{13}H_8O_5N_2$ requires C, 57·35; H, 2·9; N, 10·3%).

Reduction of 1-*Nitrophenoxazine*-3-*carboxylic Acid*.—A suspension of 1-nitrophenoxazine-3-carboxylic acid (2·5 g.) in boiling ethyl alcohol (40 c.c.) was reduced by being heated for 3 hr. with stannous chloride (9·0 g.) and concentrated hydrochloric acid (40 c.c.). After cooling the pale green product (2·4 g.) was filtered off. Recrystallisation from large quantities of distilled water containing about 1 c.c. of concentrated hydrochloric acid and a small amount of sodium dithionite gave a mixture (2·3 g.) of 1-aminophenoxazine-3-carboxylic acid and its hydrochloride, crystallising in fine pale-green needles, m. p. >340°.

Attempts to form the acetyl derivative and the *S*-benzylthiuronium salt were unsuccessful.

3-*Aminophenoxazine*-1-*carboxylic Acid Hydrochloride*.—A solution of stannous chloride (3·6 g.) in concentrated hydrochloric acid (20 c.c.) was added to 3-nitrophenoxazine-1-carboxylic acid (1·2 g.) in boiling alcohol (20 c.c.). After 2 hr.' heating the hot solution was filtered and allowed to cool, whereupon precipitation of green needles occurred. (The amount of precipitate was increased by passage of dry hydrogen chloride.) The crystalline product was dissolved in alcohol (10 c.c.), and *ca.* 2N-sodium carbonate (15 c.c.) added. The precipitated stannic hydroxide was filtered off and dilute acetic acid added to the filtrate. The free amino-acid was recrystallised from 50% hydrochloric acid, yielding fine greenish-brown needles of 3-*aminophenoxazine*-1-*carboxylic acid hydrochloride monohydrate* (1·05 g.) (Found: C, 52·1; H, 4·7; N, 9·9. $C_{13}H_{10}O_3N_2$,HCl,H_2O requires C, 52·6; H, 4·4; N, 9·45%).

1 : 3-*Diaminophenoxazine*.—1 : 3-Dinitrophenoxazine (4 g.) in glacial acetic acid (100 c.c.) was reduced with hydrogen at a maximum pressure of 5 atmospheres, in the presence of Adams's platinum oxide (0·1 g.). Reduction was complete in 5 hr. The filtered solution was concentrated under reduced pressure to 20 c.c., sealed under nitrogen, and stored in the ice-box overnight. Recrystallisation of the fine needles from 2N-sulphuric acid, containing a little sodium dithionite, yielded 1 : 3-*diaminophenoxazine sulphate* (2·6 g.), m. p. 221—223° (decomp.) (Found: S, 10·0. $C_{12}H_{11}ON_3$,H_2SO_4 requires S, 10·3%).

1-*Aminophenoxazim Picrate*.—1 : 3-Diaminophenoxazine sulphate (0·1 g.) was oxidised by passage of oxygen through its solution in water (10 c.c.) for 30 min. Saturated aqueous picric

acid solution (20 c.c.) was added and the yellowish-brown precipitate recrystallised from saturated aqueous picric acid–ethyl alcohol (3 : 4) yielding 1-*aminophenoxazim picrate*, m. p. 231—233° (decomposition appears to commence at 180°) (Found : C, 48·7; H, 2·8; N, 19·0. $C_{12}H_9ON_3,C_6H_3O_7N_3$ requires C, 49·1; H, 2·8; N, 19·1%).

5-Chloro-2 : 4-dinitroaniline.—(*a*) A stream of ammonia was passed through a mixture of 1-chloro-2 : 4 : 5-trinitrobenzene (10 g.), sodium carbonate (2·5 g.), and ethyl alcohol (50 c.c.), the temperature being kept below 50°. During the first 10 min. nearly all the solid dissolved, and the temperature then began to fall. The solution was evaporated to dryness and the residue extracted with hot 50% aqueous ethanol. The hot filtered extract, on cooling, deposited pale fawn needles of 5-chloro-2 : 4-dinitroaniline (4 g.), m. p. 184·5—185° (Found : C, 33·8; H, 2·2; N, 19·3; Cl, 16·0. Calc. for $C_6H_4O_4N_3Cl$: C, 33·1; H, 1·8; N, 19·3; Cl, 16·3%).

The insoluble residue from the alcohol extraction was crystallised from 75% acetic acid, yielding 1 : 3-diamino-4 : 6-dinitrobenzene (0·8 g.), m. p. 300—301° (Nietzki and Schedler, *Ber.*, 1897, **36**, 1667, give m. p. 300°) (Found : C, 37·0; H, 3·2. Calc. for $C_6H_6O_4N_4$: C, 36·4; H, 3·0%).

(*b*) Ammonia was passed for 10 min. into a cooled (<25°) mixture of 1-chloro-2 : 4 : 5-trinitrobenzene (10 g.) and sodium carbonate (2·5 g.) in dry benzene (20 c.c.). Next morning the precipitated yellow solid was recrystallised from 50% aqueous ethanol, yielding 5-chloro-2 : 4-dinitroaniline (6·4 g.), m. p. and mixed m. p. 184—185°.

Recrystallisation from benzene–ligroin (b. p. 60—80°) (4 : 1) yielded yellow crystals, m. p. 176—176·5° (Found : C, 33·8; H, 1·7; N, 19·0; Cl, 16·0%).

The 5-chloro-2 : 4-dinitroaniline (m. p. 184—185°) was acetylated to 5-chloro-2 : 4-dinitroacetanilide, m. p. 136·5—137° (Found : C, 37·4; H, 2·4; N, 16·1; Cl, 13·5. Calc. for $C_8H_6O_5N_3Cl$: C, 37·0; H, 2·3; N, 16·2; Cl, 13·7%.

Condensation between 1-Chloro-2 : 4 : 5-trinitrobenzene and o-Benzylaminophenol.—1-Chloro-2 : 4 : 5-trinitrobenzene (3·9 g.) and *o*-benzylaminophenol (3 g.) (Boothroyd and Clark, Part I) were stirred and heated under reflux for 4 hr. with alcohol (50 c.c.) and *ca.* 2N-sodium acetate (9 c.c.), after which *ca.* 2N-sodium hydroxide (9 c.c.) was added, and the heating and stirring continued for a further 30 min. The mixture was allowed to cool and the precipitated solids (2·2 g.) washed with dilute sodium hydroxide and water, and finally dried. Recrystallisation from ethyl acetate gave brownish-red, long rectangular plates of 10-*benzyl*-2 : 3-*dinitrophenoxazine* (1·1 g.), m. p. 238—240° (Found : C, 63·3; H, 3·8; N, 11·4. $C_{19}H_{13}O_5N_3$ requires C, 62·8; H, 3·6; N, 11·6%).

The mother liquors from the ethyl acetate recrystallisation were evaporated to dryness and the residue extracted with hot *cyclo*hexane, giving 10-*benzyl*-2-*chloro*-3-*nitrophenoxazine* (0·4 g.), as red needles, m. p. 198·5—199·5° (from *cyclo*hexane) (Found : C, 65·0; H, 3·6; N, 8·3; Cl, 10·6. $C_{19}H_{13}O_3N_3Cl$ requires C, 64·7; H, 3·7; N, 7·9; Cl, 10·1%).

Reduction of 10-Benzyl-2 : 3-dinitrophenoxazine.—Catalytic reduction and debenzylation of 10-benzyl-2 : 3-dinitrophenoxazine was attempted under conditions similar to those described in Part I, acetic acid and ethanol being used as solvents. In neither case was any identifiable material isolated, the product being apparently very readily oxidised (colour changed from light yellow through green to blue). A small amount of an impure hydrochloride, which was only partly soluble in water, was obtained from the oxidised product. Treatment with picric acid yielded a dark red precipitate, which could not, however, be recrystallised without decomposition.

The authors of this and the preceding paper are indebted to Professor J. W. McLeod, F.R.S., and Dr. R. A. Holman of the Department of Bacteriology for carrying out the biological examinations, and to Professor F. Challenger of the Department of Chemistry for the gift of 1-chloro-2 : 4 : 5-trinitrobenzene. One of them (B. B.) acknowledges a maintenance grant from Huddersfield Education Committee, during the term of which the work was carried out.

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307. *Studies in the Detoxication of Catalyst Poisons. Part IX.* Dimethylphenylphosphine.*

By E. B. Maxted and G. T. Ball.

The response of this substituted phosphine to chemical detoxication by methods which have previously been used for poisons containing sulphur has been studied. The induced non-toxicity, rather surprisingly, persists in this case only if the subsequent tests for non-toxic character are made in an oxidising system. It has also been found that dimethylphenylphosphine adsorbed on platinum can be easily and completely desorbed by the washing process which forms an alternative to chemical detoxication in the revival of poisoned catalysts.

Previous papers in this series (*J.*, 1945, 204, 763, 766; 1946, 23; 1947, 624; 1948, 1091, 1093, 1916; *J. Soc. Chem. Ind.*, 1948, **67**, 93; *Chem. and Ind.*, 1951, 242) have dealt mainly with the detoxication of catalyst poisons containing sulphur by processes involving a change in the electronic configuration of the sulphur atom from an unshielded into a shielded and therefore non-toxic state. It has now been considered of interest, first, to study the effect of similar treatment on the toxicity of a poison containing phosphorus and, secondly, to examine the efficacy of the alternative desorption or washing procedure (*J.*, 1952, 4284) when this is applied to the revivification of a catalyst poisoned by a phosphorus compound.

As a suitable available poison for this work, dimethylphenylphosphine has been taken. Alkyl- or aryl-phosphines of the type PR_3 may be regarded as phosphorus analogues of the corresponding sulphides, SR_2, and it accordingly appeared probable that a change to the corresponding oxide by an oxidative process comparable with the conversion of an organic sulphide into a non-toxic sulphone, *viz.* :

compared with :

Sulphide (unshielded, toxic type) — Sulphone (shielded, non-toxic type)

(in which the electronic configurations of the phosphorus and sulphur atoms only have been indicated) should readily lead to the required detoxication.

In order that the non-toxicity of the shielded derivative may persist under the conditions of the hydrogenation tests used to assess the degree of detoxication, it is necessary that the shielded derivative formed should not undergo reductive reversion to a toxic state under these conditions. It has been shown that this reversion does not occur with the derivatives (sulphones or sulphonic acids) formed from the common sulphur poisons, provided that the temperature used in these tests is not too high; and it seemed probable that the oxidation products of substituted phosphines also would conform to this requirement. It has, however, rather unexpectedly been found that detoxication obtained by the action of oxidants on dimethylphenylphosphine persists only if the subsequent assessment of non-toxicity is carried out in an oxidisng system instead of by catalytic hydrogenation tests.

In contrast to this anomalous behaviour of dimethylphenylphosphine with respect to chemical detoxication, the revivification of a platinum catalyst previously poisoned with dimethylphenylphospine takes place completely and without complications by desorptive

* Part VIII, *J.*, 1948, 1916.

washing with a suitable solvent. The latter method involves no preliminary change of the chemical form of the poison into a non-toxic state; but the simple desorption is assisted by a displacement of the adsorbed poison from the catalyst surface into the free liquid phase by reason of the competitive adsorption of the unsaturated substance used in the subsequent hydrogenation tests.

Experimental

The platinum catalyst was taken from a stock made from chloroplatinic acid by alkaline formate reduction. This stock had previously been washed repeatedly in a shaker, and then centrifuged before each change of the washing water, until a stable activity, unaffected by further washing, had been reached. The dimethylphenylphosphine was applied in acetic acid, as a stock solution containing 10^{-5} mole of the poison per c.c. The detoxicating reagents used in the chemical detoxication tests consisted of very dilute solutions of permolybdic or perphosphoric acid, the general procedure used in applying these being similar to that already described in detail for the detoxication of sulphur compounds (see below).

Chemical Detoxication.—In the first part of this work, the effect of the detoxication treatment was followed by hydrogenation tests carried out in a hydrogenation shaker under standardised conditions at 30°. The following results were obtained in a series of three hydrogenation runs, using (i) a poison-free blank charge containing 0·025 g. of stock platinum catalyst suspended in a 15-c.c. liquid system made up of 12·5 c.c. of acetic acid, 2 c.c. of water, and, as an unsaturated substance for hydrogenation, 0·5 c.c. of *cyclo*hexene, (ii) a similar charge poisoned by the addition of 10^{-5} mole of dimethylphenylphosphine, and (iii) a similarly poisoned charge which had, before the hydrogenation test, been treated with 3×10^{-5} mole of permolybdic acid together with three additions of 0·15 g. of hydrogen peroxide and subsequent destruction of the excess of peroxide and per-acid by heating to 100°, after which the system was cooled to 30° for the hydrogenation test. The observed rates of hydrogen adsorption in the above three tests were (i) 34, (ii) 4·2, and (iii) 8·8 c.c. per min. for the blank, poisoned, and detoxicated runs, respectively. Accordingly, the degree to which the substituted phosphine has lost its toxic character as a result of treatment with permolybdic acid, under conditions which have previously been found to lead to the complete detoxication of a sulphur-containing poison, is not very great. A similar result was obtained in a further series of three runs in which perphosphoric acid was substituted for permolybdic acid as the detoxicating reagent.

Dimethylphenylphosphine is known to be oxidised easily; and it would be expected that the resulting oxide would resist subsequent reduction. However, since its failure to respond substantially to the above detoxication treatment might be due either to incomplete oxidation to a shielded derivative or to the reversion of this derivative to a toxic form during the hydrogenation process, it was of interest to try to detoxicate this poison with a per-acid as before and then to assess the degree of the response by means of a catalytic reaction carried out in an oxidising system, namely, for the decomposition of hydrogen peroxide, in place of by a hydrogenation test.

In this series, the system to be detoxicated was contained in a reaction pipette provided with a separate reservoir by means of which the charge of hydrogen peroxide required for the activity test could be added without opening the system. The detoxication preceding the test was carried out as before, namely, by adding to the poisoned system, at room temperature, a reagent containing a small quantity of perphosphoric or permolybdic acid in the presence of hydrogen peroxide and subsequently destroying the excess of per-acid and peroxide by heating to 100° until no more oxygen was evolved, the pipette being then closed by plugging in the small reservoir containing the further charge of hydrogen peroxide. This closed system was immersed in a thermostat at 20° and, after the reservoir-plug had been turned to admit the additional peroxide to the detoxicated charge, the pipette was shaken gently, by means of a mechanical shaker operating at a constant speed, in connection with a gas burette in which the rate of evolution of oxygen corresponding with the decomposition of the hydrogen peroxide during the test could be measured. It was found that, in order to obtain convenient rates of oxygen evolution, a somewhat larger charge than that used in the hydrogenation tests was preferable; and, in this series, the volume of liquid originally contained in the pipette was 58 c.c., to which was added, from the reservoir, a further charge made up of 2 c.c. of hydrogen peroxide (approx. 100-vol.) and 5 c.c. of water.

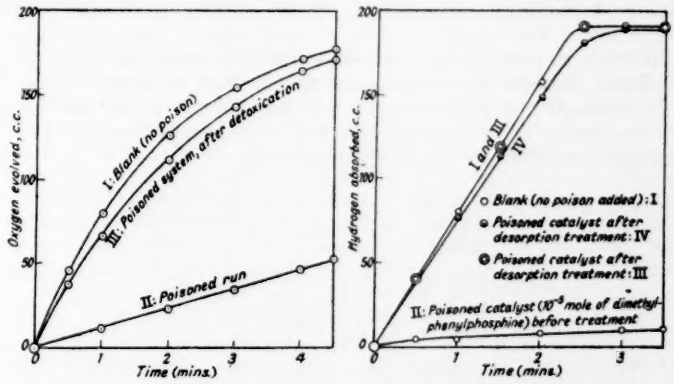
Results in the usual series of three tests, consisting of a blank run, a poisoned run, and a run after the detoxication of the poisoned system, are summarised in Fig. 1. In this, Curve II is

the poisoned run obtained with a system containing $2{\cdot}5 \times 10^{-4}$ mole of dimethylphenylphosphine in 8 c.c. of acetic acid, 50 c.c. of water, and 0·025 g. of platinum catalyst, the testing charge of 7 c.c. of dilute hydrogen peroxide being added as already described. Curve III was given by a similarly poisoned system after this had been detoxicated by adding $3{\cdot}5 \times 10^{-5}$ mole of perphosphoric acid together with three additions of 0·15 g. (*ca.* 5×10^{-3} mole) of hydrogen peroxide and subsequent destruction of the excess of per-acid and hydrogen peroxide by heat before placing the pipette in the thermostat and adding the 7-c.c. charge of hydrogen peroxide for the activity test. In the blank run (Curve I) the poison was omitted; and, save for this omission, the system and its subsequent treatment were identical with those used for Curve III.

These results were confirmed by a further series of three tests in which permolybdic acid was used as the detoxicating reagent in place of perphosphoric acid and which gave curves approximating to those of Fig. 1. It will be seen that, although complete detoxication was not quite reached, the degree of disappearance of the toxicity of the poison as a result of the detoxication treatment is far greater when the subsequent activity test involves hydrogen peroxide decomposition than when catalytic hydrogenation is used for this assessment. As already stated, this result differs from those obtained with sulphur poisons.

FIG. 1. *Detoxication of dimethylphenylphosphine.* (Hydrogen peroxide decomposition tests.)

FIG. 2. *Removal of dimethylphenylphosphine from platinum.*


Oxygen evolved, c.c.
Time (mins.)
I: Blank (no poison)
III: Poisoned system, after detoxication
II: Poisoned run
Hydrogen absorbed, c.c.
I and III
IV
Blank (no poison added): I
Poisoned catalyst after desorption treatment: IV
Poisoned catalyst after desorption treatment: III
II: Poisoned catalyst (10^{-5} mole of dimethylphenylphosphine) before treatment

Removal of Dimethylphenylphosphine from Platinum Catalysts by Desorption.—It was found that dimethylphenylphosphine can be easily and completely removed by the desorptive washing method from catalysts inactivated by this poison.

In this section of the work, 0·025 g. of platinum was suspended in a hydrogenation system consisting of 9 c.c. of acetic acid and 1 c.c. of *cyclo*hexene and poisoned by the addition of 10^{-5} mole of dimethylphenylphosphine. The rate at which this poisoned catalyst induces hydrogenation was then tested in a hydrogenation shaker at 30°. Curve II of Fig. 2 gives this activity compared with the activity of a similar charge of unpoisoned catalyst in a blank run (Curve I) in which the poison was omitted. In order to examine the ease with which this poison can be removed from the platinum by desorption, the catalyst, after having been poisoned with 10^{-5} mole of dimethylphenylphosphine, was separated from the supernatant liquid by centrifuging and decantation and washed for two successive periods of 30 min. each, first with 10 c.c. of acetic acid and then (after again centrifuging and decanting off the liquid) with a normal hydrogenation charge consisting of 10 c.c. of acetic acid containing 1 c.c. of *cyclo*hexene, these washings being carried out by shaking in a closed pipette in the absence of hydrogen. Admitting hydrogen and carrying out the hydrogenation test by means of which the recovery in the activity of the platinum was assessed gave Curve III, showing a complete restoration of the activity of the previously poisoned catalyst: indeed, in a further test with a similarly poisoned catalyst, an almost complete extraction of the poison from the catalyst was reached even after one change of the supernatant liquid (Curve IV).

We thank Mr. G. E. Coates for providing the dimethylphenylphosphine.

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308. *The Structure of Native Poly-D-glutamic Acid. Part IV.* The Synthesis of Poly-L-glutamine and the Hofmann Degradation thereof.*

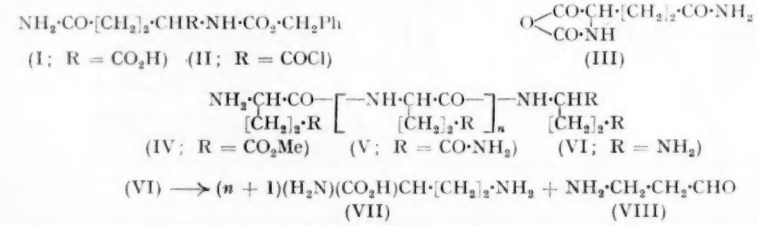
By V. Bruckner, J. Kovács, and K. Kovács.

Methyl α-poly-L-glutamate was converted into poly-L-glutamine, which was degraded by Hofmann's method. Acid hydrolysis then gave αγ-diaminobutyric acid. This corroborates the previous conclusion that in native poly-D-glutamic acid α-glutamyl bonds cannot predominate, since analogous treatment of the polyamide prepared from native poly-acid gave no detectable αγ-diaminobutyric acid.

The isolation of β-formylpropionic acid but not of αγ-diaminobutyric acid from the acid hydrolysate of the Curtius-degraded polyhydrazide or the Hofmann-degraded polyamide, respectively, of *B. subtilis* poly-D-glutamic acid (Kovács and Bruckner, *Research*, 1952, **5**, 194; *J.*, 1952, 4255; Bruckner, Kovács, and Nagy, *J.*, 1953, 148) suggests the predominance of γ-glutamyl links in that polypeptide. This result appears to be further substantiated by the analogous degradation of the synthetically prepared polyamide of α-poly-L-glutamic acid (poly-L-glutamine), which affords αγ-diaminobutyric acid, as expected.

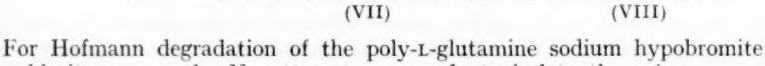
Our first attempt to prepare poly-DL-glutamine (V) directly from carbobenzyloxy-DL-glutamine (I) failed, because by the conventional method no intermediates (II and III) were isolated, although the resinous end product showed a distinct biuret reaction.

However, treatment of a synthetic methyl α-poly-L-glutamate (IV) with liquid ammonia afforded a well-defined poly-L-glutamine (V).



(I; R = CO_2H) (II; R = COCl) (III)

(IV; R = CO_2Me) (V; R = $CO{\cdot}NH_2$) (VI; R = NH_2)



(VII) (VIII)

For Hofmann degradation of the poly-L-glutamine sodium hypobromite or sodium hypochlorite was used. No attempt was made to isolate the primary product of the degradation (VI), although this may be of interest in connection with the structure of polymyxine. Rather, the solution was acidified with hydrochloric acid and then hydrolysed. From the hydrolysate αγ-diaminobutyric acid (VII) was isolated as the diflavianate and the dipicrate. Although the yield did not exceed 19·5%, the crucial point is that this treatment of the same small quantity of the material under exactly the same conditions as in the degradation of the polyamide of native poly-D-glutamic acid (Bruckner, Kovács, and Nagy, *loc. cit.*) readily afforded αγ-diaminobutyric acid, whence it follows that native poly-D-glutamic acid cannot contain an appreciable proportion of α-glutamyl bonds.

The other product (VIII) of the hydrolysis is unstable and is formed in such small quantity that it cannot be assayed.

Experimental

Carbobenzyloxy-DL-glutamine (I).—To an ice-cooled, stirred solution of DL-glutamine (10 g.) in 3·33% sodium hydrogen carbonate solution (180 ml.) benzyl chloroformate (25 g.) and sodium hydrogen carbonate (20 g.) were added portionwise (15 minutes). Stirring was continued for 1 hour with cooling, and for another 2 hours at room temperature. The excess of benzyl chloroformate was extracted with ethyl acetate (2 × 50 ml.), and the solution made acid to Congo-red, and then kept in the ice-box. The *product* (I) (12 g.; m. p. 142—143°), collected, washed

* Part III, *J.*, 1953, 148.

with water, and recrystallized from ethyl acetate–petrol, formed colourless, glistening plates (9 g.), m. p. 144—145° (Found: C, 55·4; H, 5·75. $C_{13}H_{16}O_5N_2$ requires C, 55·7; H, 5·75%). Bergmann and Zervas (*Ber.*, 1932, **65**, 1192) report for carbobenzyloxy-L-glutamine m. p. 137°.

Attempted Synthesis and Polymerization of 4-2′-Carbamoylethyloxazolid-2 : 5-dione (III).—A mixture of carbobenzyloxy-DL-glutamine (5 g.), acetic anhydride (20 ml.), and purified thionyl chloride (2·5 ml.; freshly distilled from linseed oil and from quinoline) was refluxed on the steam-bath with exclusion of moisture. Gas was freely evolved and the substance dissolved in 20 minutes. Solvent and excess of reagent were removed *in vacuo*, and the remaining yellow oil was warmed (receiver cooled with liquid air) at 100°/0·001 mm. for 2 hours and then at 130° for another 2 hours (oil-bath). There was much foaming and a resin was formed [3·36 g. Calc. for formation of (III): 2·5 g.]. The product gave a distinct biuret reaction.

Poly-L-glutamine (V).—Finely powdered synthetic methyl α-poly-L-glutamate (12 g.) (Hanby, Waley, and Watson, *J.*, 1950, 3239; Coleman, *J.*, 1951, 2294; J. Kovács, Bruckner, and K. Kovács, *J.*, 1953, **145**) was kept with liquid ammonia (200 ml.; distilled from metallic sodium) in a sealed tube at room temperature for 1 week, with occasional shaking, and gradually crumbled. The ammonia was removed, and the product washed five times with hot water (total, 200 ml.), then dried (P_2O_5) *in vacuo*. It (10·5 g.) was finely powdered, and the above treatment with ammonia was repeated. The *polymer*, washed with hot water and dried to constant weight at 100°/1 mm., was a colourless powder (9 g.), giving a strong biuret reaction [Found: C, 46·9; H, 6·25; total N, 20·4; amido- and ammonium N, 10·4; OMe, 1·3. $(C_5H_8O_2N_2)_n$ requires C, 46·9; H, 6·3; total N, 21·9; amido-N, 10·9; OMe, 0%]. The same product was obtained when reaction was effected at 60°.

Evaporation of the washings *in vacuo* gave an amorphous glass readily soluble in water and giving a strong biuret reaction. Analysis (Found: C, 43·0; H, 6·6; total N, 20·4; OMe, 0·4%) indicated partial hydrolysis of the polyamide extracted by the hot water on washing (cf. Schulze and Trier, *Ber.*, 1912, **45**, 257, concerning the hydrolysis of glutamine).

Degradation of Poly-L-glutamine.—(*a*) To a freshly prepared sodium hypobromite solution (0·6 ml. of bromine in 20 ml. of 3N-sodium hydroxide), finely powdered poly-L-glutamine (1·3 g.) was added. On being shaken, complete dissolution occurred (20 minutes), and the solution was then immersed in a bath at 90° for 15 minutes (slight odour of ammonia), acidified with concentrated hydrochloric acid, and evaporated *in vacuo*. After dissolution of the solid residue in concentrated hydrochloric acid (30 ml.), and removal of precipitated inorganic salts, the filtrate was refluxed for 20 hours, then evaporated *in vacuo*; the residue was redissolved in a small quantity of water, and the solution again evaporated. For complete removal of hydrochloric acid this double procedure was repeated. The residue was then dissolved in saturated aqueous picric acid (30 ml.), and next morning the solid was collected, washed with a little water and recrystallized from water (3 ml.), affording glistening yellow plates (0·4 g., 13·3%), m. p. 189° alone or mixed with an authentic specimen of αγ-diaminobutyric acid dipicrate (Found: C, 33·6; H, 3·0. Calc. for $C_{16}H_{16}O_{16}N_8$: C, 33·3; H, 2·8%).

(*b*) Finely powdered poly-L-glutamine (325 mg.) was treated with a sodium hypobromite solution (one-quarter of above quantities) and worked up as under (*a*) except that refluxing with concentrated hydrochloric acid was reduced to 8 hours. The hydrolysate was evaporated *in vacuo*, and the residue redissolved in water (4 ml.) in which flavianic acid (1·5 g.) was then dissolved with gentle warming. After cooling, the crystalline precipitate was collected and washed with water (two portions, total 4 ml.), methanol, and ether. The yellow needles of the product (370 mg., 19·5%; m. p. 232°) were once recrystallized from water, and then melted at 239° alone or mixed with an authentic specimen of αγ-diaminobutyric acid diflavianate.

(*c*) Finely powdered polyamide (100 mg.) was treated with 3·2% sodium hypochlorite solution (prepared from 3·7 ml. of 2·5N-sodium hydroxide) as under (*a*), and hydrolysis was similarly effected. The residue of the evaporated hydrolysate was dissolved in water (3 ml.), the solution again evaporated under diminished pressure, and this treatment repeated. The residue was dissolved in water (0·5 ml.), and saturated aqueous flavianic acid solution (2 ml.) was added. After two days the precipitate was collected, washed, and dried as usual, the yield being 95 mg. (16·3%). The m. p. (233°) was raised by one recrystallization from water to 239° and remained undepressed on admixture with αγ-diaminobutyric acid diflavianate, m. p. 239°.

(*d*) Poly-L-glutamine (50 mg.) was treated with alkaline sodium hypochlorite solution as under (*c*), and the subsequent acid hydrolysis was effected in exactly the same way as after the Hofmann degradation of the polyamide of native poly-D-glutamic acid (Bruckner, Kovács, and Nagy, *loc. cit.*). To the alkaline solution (2·1 ml.) resulting from the reaction, concentrated hydrochloric acid (10 ml.) was added, and the solution was refluxed for 30 minutes, cooled to

room temperature, and filtered from deposited inorganic salts; the filtrate was evaporated *in vacuo*, the residue redissolved in water, the solution again evaporated under diminished pressure, and saturated aqueous flavianic acid solution (1 ml.) added. After two days the crystals were collected and washed as usual; yield, 10 mg., m. p. 202—210°, raised by recrystallization from four drops of water to 233°, undepressed on admixture with authentic αγ-diaminobutyric acid diflavianate, m. p. 239°.

(*e*) The following experiment shows that under conditions in which degradation of the amide of native poly-D-glutamic acid affords the maximal yield of β-formylpropionic acid, poly-L-glutamine does not produce this degradation product. Finely powdered poly-L-glutamine (50 mg.) was shaken with 1·40% alkaline sodium hypochlorite solution (2·1 ml.) for 1 hour, and the mixture warmed to 50° for 10 minutes. Complete dissolution did not occur, and no evolution of ammonia was observed (contrast behaviour of the amide of native poly-D-glutamic acid). The mixture was then refluxed with concentrated hydrochloric acid (10 ml.) for 30 minutes, and evaporated, the residue taken up in a small quantity of water, and the solution again evaporated. The residue completely dissolved in 12 drops of a freshly prepared saturated solution of *p*-nitrophenylhydrazine in N-hydrochloric acid. Neither on subsequent warming, nor on cooling and seeding with β-formylpropionic acid *p*-nitrophenylhydrazone was any separation of solid observed, whereas degradation of the amide of native poly-D-glutamic acid (50 mg.) under exactly identical conditions afforded 32 mg. of β-formylpropionic acid *p*-nitrophenylhydrazone.

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309. *Benz-1 : 3-oxathioles, Benz-1 : 4-oxathien, and αω-Bisarylthioalkanes.*

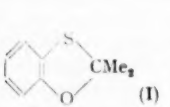
By DOUGLAS GREENWOOD and HERBERT A. STEVENSON.

With aliphatic aldehydes or ketones, and with carbonyl chloride, *o*-hydroxybenzenethiol gives respectively 2-alkyl- or 2 : 2-dialkyl-benz-1 : 3-oxathioles (*e.g.*, I), and benz-1 : 3-oxathiol-2-one (III). With alkylene dibromides the thiol forms bis-*o*-hydroxyphenylthioalkanes, though when ethylene dibromide is used, benz-1 : 4-oxathien (VI) is also obtained. *o*-Hydroxyphenylthioacetic acid, from *o*-hydroxybenzenethiol and chloroacetic acid, readily cyclises to 2-ketobenz-1 : 4-oxathien (VII).

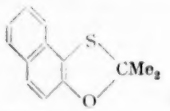
Some of these reactions have been extended to other hydroxyarenethiols, including 2-hydroxynaphthalene-1-thiol.

ALTHOUGH the action of sulphur on sodium phenoxide (Haitinger, *Monatsh.*, 1883, **4**, 166; Palmer, U.S.P. 2,004,728) gives poor yields of a product that is difficult to purify, *o*-hydroxybenzenethiol can be obtained in quantity by a modification of Friedlander and Mauthner's method (*Z. Farben- Textil-chem.*, 1904, **3**, 333; *Chem. Zentr.*, 1904, II, 1176) involving the diazotisation of *o*-aminophenol and reaction with potassium ethyl xanthate. A preliminary study of 5- and 6-membered ring compounds derived from this thiol and from 2-hydroxynaphthalene-1-thiol (Stevenson and Smiles, *J.*, 1930, 1743) has been made.

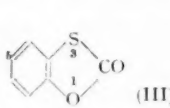
Under the influence of hydrogen chloride, *o*-hydroxybenzenethiol condenses with aliphatic aldehydes or ketones, to give 2-alkyl- or 2 : 2-dialkyl-benz-1 : 3-oxathioles (*e.g.*, I), together with alkali-soluble by-products, presumably bis-*o*-hydroxyphenylthio-



(I)



(II)



(III)

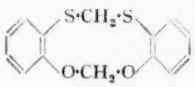
alkanes. 2-Hydroxynaphthalene-1-thiol and acetone similarly yielded 2 : 2-dimethylnaphtho-(1′ : 2′-4 : 5)-1 : 3-oxathiole (II). Attempts to extend the reaction to aromatic aldehydes and ketones have so far not given pure 2-arylbenz-1 : 3-oxathioles.

The reaction is analogous to the preparation of substituted benzo-1 : 3-dithioles from *o*-dimercaptobenzene and aromatic aldehydes and ketones [Guha and Chakladar, *J. Indian Chem. Soc.*, 1925, **2**, 318; Hurtley and Smiles, *J.*, 1926, (*a*) 1821, (*b*) 2263; (*c*) 1927, 534]. Slooff (*Rec. Trav. chim.*, 1935, **54**, 995) prepared the analogous 2 : 2-dialkylbenzo-1 : 3-dioxoles by reaction of catechol with ketones in the presence of phosphoric oxide.

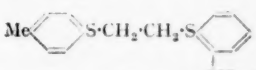
Hurtley and Smiles [*locc. cit.*, (*a*), (*c*)] obtained interesting results on oxidising benzo-1 : 3-dithioles. They found, for example, that 2-phenylbenzo-1 : 3-dithiole and nitric acid yielded a nitrate which on hydrolysis gave 2-phenylbenzo-1 : 3-dithiole 2-oxide. This compound behaved as a pseudo-base, giving sulphonium salts with acids. It is remarkable that these authors observed no normal oxidation products of these cyclic sulphides. We have found that the oxathioles (I) and (II) give sulphoxides on mild oxidation with hydrogen peroxide. Oxidation with neutral permanganate gave sulphones.

Kaufmann and Weber (*Arch. Pharm.*, 1929, **267**, 192) obtained 5-methylbenz-1 : 3-oxathiol-2-one from *p*-cresol and thiocyanogen by ring-closure of the 4-methyl-2-thiocyanatophenol to 2-imino-5-methylbenz-1 : 3-oxathiole followed by acid hydrolysis, and Stevenson and Smiles (*loc. cit.*) and Werner (U.S.P. 2,332,418) similarly prepared a number of analogues. However, the parent compound, benz-1 : 3-oxathiol-2-one cannot be prepared in this way because a substituent is required in the phenol nucleus in order to direct the thiocyanato-group into an *ortho*-position. Benz-1 : 3-oxathiol-2-one (III) has now been obtained by two methods. (1) The *o*-thiocyanato-group was introduced by reaction of diazotised *o*-aminophenol with cuprous thiocyanate. Ring-closure and hydrolysis as before gave the compound in small yield. (2) A much better yield was obtained by the direct action of carbonyl chloride on *o*-hydroxybenzenethiol. Similarly, thiocarbonyl chloride gave benz-1 : 3-oxathiole-2-thione, previously isolated by Friedlander and Mauthner (*loc. cit.*) as a by-product of the reaction between diazotised *o*-aminophenol and potassium ethyl xanthate. Hurtley and Smiles [*loc. cit.*, (*a*)] obtained benzo-1 : 3-dithiol-2-one and benzo-1 : 3-dithiole-2-thione by the action of carbonyl chloride and carbon disulphide respectively on *o*-dimercaptobenzene, and found that benzo-1 : 3-dithiol-2-one could be mononitrated but did not afford simple oxidation products owing to disruption of the heterocyclic ring. Benz-1 : 3-oxathiol-2-one (III) behaves analogously, giving a (?5-)nitro-derivative.

Several new bishydroxyarylthioalkanes have been prepared by condensation of *o*- and *p*-hydroxybenzenethiols and 2-hydroxynaphthalene-1-thiol with alkylene dibromides. Those from *o*-hydroxybenzenethiol were acetylated and then oxidised to disulphones by usual methods. Bis-*o*-hydroxyphenylthiomethane, $(o\text{-}OH\cdot C_6H_4\cdot S)_2CH_2$, was condensed with a further equivalent of methylene dibromide, giving 4 : 5-9 : 10-dibenzo-1 : 3-dioxa-6 : 8-dithia*cyclo*deca-4 : 9-diene (IV). Condensation of *p*-tolylthioethyl bromide (from toluene-*p*-thiol and ethylene dibromide) with *o*-hydroxybenzenethiol gave 1-*o*-hydroxyphenylthio-2-*p*-tolylthioethane, isolated as the tetrahydrate (V) of its sodium salt.



(IV)



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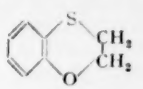
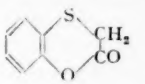
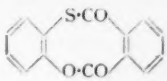


(VI)

o-Hydroxybenzenethiol and ethylene dibromide invariably gave as the main product 1 : 2-bis-*o*-hydroxyphenylthioethane, but under appropriate conditions a small yield of benz-1 : 4-oxathien (VI) was also obtained. An attempt to synthesise benz-1 : 3-oxathiole by a similar reaction between *o*-hydroxybenzenethiol and methylene dibromide failed, as only bis-*o*-hydroxyphenylthiomethane could be isolated.



(VII)



(VIII)

Benz-1 : 4-oxathien (VI) readily gave a sulphoxide on oxidation, and more vigorous neutral oxidation yielded a sulphone.

Condensation of *o*-hydroxybenzenethiol with one equivalent of chloroacetic acid gave an oil, probably *o*-hydroxyphenylthioacetic acid, *o*-$OH{\cdot}C_6H_4{\cdot}S{\cdot}CH_2{\cdot}CO_2H$ (Friedlander, *Annalen*, 1907, **351**, 414). This compound readily gives 2-ketobenz-1 : 4-oxathien (VII) on attempted distillation (or when heated). *o*-Hydroxybenzenethiol and two equivalents of chloroacetic acid gave *o*-carboxymethylthiophenoxyacetic acid.

Several new *OS*-esters of *o*-hydroxybenzenethiol and of other hydroxyarenethiols are reported, including the cyclic compound (VIII) prepared by means of phthaloyl chloride.

Experimental

o-Hydroxybenzenethiol.—The yield of this compound obtained by Friedlander and Mauthner's method (*loc. cit.*) was improved by addition of further quantities of zinc dust (40 g.) and concentrated hydrochloric acid (120 c.c.) to the residue after steam-distillation. Continuation of the steam-distillation then gave more thiol by reduction of the disulphide present as a by-product. Yields of 30—70% were obtained, varying with the quality and age of the commercial batches of *o*-aminophenol.

If this modification was not applied, di-*o*-hydroxyphenyl disulphide could be isolated as follows. The residue after steam-distillation was extracted with ether, dried, and distilled at 2 mm., the viscous yellow oil of b. p. 160—170° being collected. Trituration with 2N-sodium carbonate gave the monosodium salt, which crystallised from ethanol as prisms of the *pentahydrate*, m. p. 136° (decomp.) [Found: C, 39·55; H, 5·4; H_2O (Karl Fischer), 22·7. $C_{12}H_9O_2S_2Na,5H_2O$ requires C, 39·8; H, 5·25; H_2O, 24·9%]. Haitinger (*loc. cit.*) does not give the m. p. of his hexahydrate of this compound obtained in a similar manner.

The disulphide was also obtained by oxidation of the thiol. Passage of a slow stream of air for 48 hr. through a solution of *o*-hydroxybenzenethiol (6 g.) in ethanol (25 c.c.) containing ammonia (1 c.c., *d* 0·880), and isolation as above, gave a good yield of the monosodium salt. Acetylation gave *di-o-acetoxyphenyl disulphide*, needles, m. p. 57° after recrystallisation from light petroleum (b. p. 60—80°) (Found: C, 57·35; H, 3·8. $C_{16}H_{14}O_4S_2$ requires C, 57·5; H, 4·2%).

Preparation of Benz-1 : 3-oxathioles.—Dry hydrogen chloride was passed into a solution of *o*-hydroxybenzenethiol (18 g.) in acetone (60 c.c., large excess) for 2 hr. without control of temperature, and then for 30 min. at 0°. A red colour developed at the end of the reaction. The mixture was poured into dilute alkali, and the oil extracted with ether, dried, and fractionated. **2 : 2-*Dimethylbenz*-1 : 3-*oxathiole*** (9·6 g.) was collected at 60°/1·5 mm., and had a sweet ester-like smell (Found: C, 64·65; H, 5·75%; *M*, 160. $C_9H_{10}OS$ requires C, 65·1; H, 6·0%; *M*, 166). Acidifying the alkaline solution and again extracting with ether gave about 5 c.c. of oil, but on distillation, no fraction of constant b. p. was obtained.

o-Hydroxybenzenethiol (18 g.) and ethyl methyl ketone (60 c.c.) similarly gave **2-*ethyl*-2-*methylbenz*-1 : 3-*oxathiole*** (15·4 g.), b. p. 85°/3 mm. (Found: C, 66·7; H, 6·65. $C_{10}H_{12}OS$ requires C, 66·7; H, 6·7%).

2-Hydroxynaphthalene-1-thiol (17 g.) and acetone (150 c.c.) similarly gave **2 : 2-*dimethylnaphtho*(1′ : 2′-4 : 5)-1 : 3-*oxathiole*** (8·7 g.), b. p. 135—136°/2·5 mm. (Found: C, 72·1; H, 5·6. $C_{13}H_{12}OS$ requires C, 72·2; H, 5·6%).

o-Hydroxybenzenethiol (24 g.) and acetaldehyde (100 c.c.) reacted similarly. Distillation of the products gave paraldehyde, followed by **2-*methylbenz*-1 : 3-*oxathiole*** (9·6 g.), b. p. 70—74°/3 mm. (Found: C, 64·1, 63·0; H, 5·6, 5·85. C_8H_8OS requires C, 63·2; H, 5·3%).

Oxidation of Benz-1 : 3-oxathioles.—**2 : 2-Dimethylbenz-1 : 3-oxathiole** (1 g.) and hydrogen peroxide (0·8 c.c.; 30%), kept in acetic acid (25 c.c.) at room temperature for 5 days and then diluted with water, gave an oil which solidified after ether-extraction. Recrystallisation from light petroleum (b. p. 60—80°) gave the *sulphoxide*, prisms (0·7 g.), m. p. 38° (Found: C, 59·7; H, 5·45. $C_9H_{10}O_2S$ requires C, 59·3; H, 5·5%). Excess of hydrogen peroxide in acetic acid at 100° appeared to cause decomposition, and no product was isolated.

2 : 2-Dimethylbenz-1 : 3-oxathiole (0·5 g.) was suspended in a little water containing magnesium sulphate (2 g.), and the theoretical amount of potassium permanganate (210 c.c.; 0·1N) added during 1 hr. at 80—85°. After treatment with sulphur dioxide, chloroform-extraction gave an oil which crystallised. Recrystallisation from light petroleum (b. p. 60—80°) gave the *sulphone*, needles (0·1 g.), m. p. 75° (Found: C, 54·35; H, 4·65. $C_9H_{10}O_3S$ requires C, 54·5; H, 5·05%).

2 : 2-Dimethylnaphtho(1′ : 2′-4 : 5)-1 : 3-oxathiole was converted similarly into its *sulphoxide*, needles, m. p. 134° [from light petroleum (b. p. 60—80°)] (Found: C, 67·4; H, 5·15. $C_{13}H_{12}O_2S$

requires C, 67·2; H, 5·2%), and *sulphone*, needles (from ethanol), m. p. 155° (Found : C, 63·2; H, 4·55. $C_{13}H_{12}O_3S$ requires C, 62·9; H, 4·8%).

Benz-1 : 3-oxathiol-2-one.—Method 1. *o*-Aminophenol (100 g.) was diazotised, and treated with cuprous thiocyanate (223 g.) and sodium thiocyanate (180 g.). The mixture was warmed slowly until evolution of nitrogen was complete, refluxed for 1 hr. to hydrolyse the 2-imine, and then steam-distilled. The distillate was extracted with ether, and the ether dried and evaporated. The residue on distillation at 2·5 mm. yielded phenol (5 g.), followed by the *product* (20·5 g.) at 93—96°. This had m. p. 26° (Found : C, 55·1; H, 2·5. $C_7H_4O_2S$ requires C, 55·3; H, 2·6%).

Method 2. Carbonyl chloride was passed into a solution of *o*-hydroxybenzenethiol (6·5 g.) in 0·5N-sodium hydroxide (520 c.c.). Benz-1 : 3-oxathiol-2-one, precipitated as an oil, was extracted with ether, dried, and distilled (b. p. 94°/2 mm., m. p. 26°; 4·9 g.).

Benz-1 : 3-oxathiol-2-one (1 g.) and nitric acid (10 c.c.; *d* 1·4) were refluxed for 2½ hr., then cooled and diluted with water. One recrystallisation from dilute acetic acid and two from ethanol then gave long colourless needles of (?5-)*nitrobenz-1 : 3-oxathiol-2-one*, m. p. 182—183° (Found : N, 7·1. $C_7H_3O_4NS$ requires N, 7·1%).

Benz-1 : 3-oxathiole-2-thione.—A solution of *o*-hydroxybenzenethiol (20 g.) and sodium hydroxide (16 g.) in water (250 c.c.) was shaken with a slight excess of thiocarbonyl chloride (15 c.c.) for 3 hr. The oily product was separated and recrystallised four times from ethanol, giving yellow needles (5·8 g.), m. p. 97—98°. Friedlander and Mauthner (*loc. cit.*) give m. p. 99·5°.

Bisarylthioalkanes.—*o*-Hydroxybenzenethiol (40 g.), methylene dibromide (27·6 g.), and sodium ethoxide (24 g.) were refluxed in ethanol (600 c.c.) for 3 hr. Cooling and addition of dilute hydrochloric acid gave an oil which crystallised. Two recrystallisations from light petroleum (b. p. 60—80°) gave needles (24 g.) of *bis-o-hydroxyphenylthiomethane*, m. p. 67—68° (Found : C, 59·5, 59·05; H, 4·4, 4·2. $C_{13}H_{12}O_2S_2$ requires C, 59·1; H, 4·5%). Acetylation gave *bis-o-acetoxyphenylthiomethane*, prisms, m. p. 52° [from light petroleum (b. p. 60—80°)] (Found : C, 58·65; H, 4·6. $C_{17}H_{16}O_4S_2$ requires C, 58·6; H, 4·6%). Condensation of bis-*o*-hydroxyphenylthiomethane with a further equivalent of methylene dibromide gave 10% of a pale yellow powder insoluble in alkali. After one recrystallisation from dilute acetic acid and four from dilute ethanol, the product, probably 4 : 5-9 : 10-*dibenzo*-1 : 3-*dioxa*-6 : 8-*dithia*cyclo-*deca*-4 : 9-*diene*, had m. p. 151° (Found: C, 60·4; H, 4·4. $C_{14}H_{12}O_2S_2$ requires C, 60·9; H, 4·35%).

Similarly, *o*-hydroxybenzenethiol (20 g.) and ethylene dibromide (16·6 g.) gave 1 : 2-*bis*-o-*hydroxyphenylthioethane*, needles (16·6 g.), m. p. 108° [from light petroleum (b. p. 60—80°)] (Found : C, 60·7; H, 5·1%; *M*, 272·5. $C_{14}H_{14}O_2S_2$ requires C, 60·4; H, 5·0%; *M*, 278). Acetylation gave 1 : 2-*bis*-o-*acetoxyphenylthioethane* (94%), plates, m. p. 79° [from light petroleum (b. p. 60—80°)] (Found : C, 60·15; H, 4·75. $C_{18}H_{18}O_4S_2$ requires C, 59·7; H, 5·0%). Oxidation of this compound (34 g.) with hydrogen peroxide (65 c.c., 30%) in acetic acid (350 c.c.) at 100° for 4 hr. gave 1 : 2-*bis*-o-*acetoxyphenylsulphonylethane* (11·2 g.), plates, m. p. 204—205° (from 50% acetic acid) (Found : C, 50·3, 50·8; H, 4·3, 4·2. $C_{18}H_{18}O_8S_2$ requires C, 50·7; H, 4·2%).

o-Hydroxybenzenethiol (11·2 g.) and 1 : 10-dibromodecane (13·5 g.) gave 1 : 10-*bis*-o-*hydroxyphenylthiodecane* as an oil characterised as its *diacetate* (19 g.), plates, m. p. 65—66° after three recrystallisations from light petroleum (b. p. 60—80°) (Found : C, 65·4, 66·1; H, 6·9, 7·25. $C_{26}H_{34}O_4S_2$ requires C, 65·8; H, 7·2%).

p-Hydroxybenzenethiol (12 g.) and ethylene dibromide (9·6 g.) gave 1 : 2-*bis*-p-*hydroxyphenylthioethane* (7·2 g.), an amorphous powder, m. p. 168° (from chloroform) (Found : C, 60·05; H, 5·1. $C_{14}H_{14}O_2S_2$ requires C, 60·4; H, 5·0%).

2-Hydroxynaphthalene-1-thiol (15·2 g.) and ethylene dibromide (8·2 g.) gave 1 : 2-*bis*-(2-*hydroxy*-1-*naphthylthio*)*ethane* (12 g.), needles, m. p. 155° (from ethanol) (Found : C, 70·05; H, 5·2. $C_{22}H_{18}O_2S_2$ requires C, 69·8; H, 4·8%).

When toluene-*p*-thiol (35 g.), sodium ethoxide (20 g.), and ethylene dibromide (30·5 g.) were refluxed in acetone (500 c.c.) for 2 hr., only a 25% yield of 1 : 2-bis-*p*-tolylthioethane was obtained. The main product, isolated by further addition of water to the reaction mixture, was an oil, b. p. 132°/4 mm., 118°/2 mm., probably 2-p-*tolylthioethyl bromide* (Found : C, 48·8; H, 4·8. $C_9H_{11}BrS$ requires C, 46·8; H, 4·8%). The high carbon content was probably due to presence of 2-*p*-tolylthioethanol (Calc. for $C_9H_{12}OS$: C, 64·3; H, 7·1%). The identity of the compound was verified by condensation with a second equivalent of toluene-*p*-thiol, a 98% yield of 1 : 2-bis-*p*-tolylthioethane being obtained (m. p. and mixed m. p. 80°). Condensation of 2-*p*-tolylthioethyl bromide (8·4 g.) with *o*-hydroxybenzenethiol (4·2 g.) gave a solid

melting at *ca.* 20°. Trituration with 2N-sodium hydroxide gave the sodium salt of 1-*o*-hydroxyphenylthio-2-*p*-tolylthioethane as a *tetrahydrate*, which formed plates (7·0 g.), m. p. 79—80°, from benzene [Found : C, 48·75; H, 6·4; H_2O (Karl Fischer), 15·15. $C_{15}H_{15}OS_2Na,4H_2O$ requires C, 48·65; H, 6·2; H_2O, 19·5%].

Bis-*p*-tolylthiomethane (18 g.) was obtained from toluene-*p*-thiol (20 g.) and methylene dibromide (15 g.) as needles, m. p. 32° (from ethanol) (Found : C, 69·1; H, 5·9. Calc. for $C_{15}H_{16}S_2$: C, 69·2; H, 6·15%). Fromm, Forster, and von Scherschewitzki (*Annalen*, 1912, **394**, 348) described this compound as an oil.

Benz-1 : 4-*oxathien*.—An attempt was made to prepare this compound by way of 2-*o*-hydroxyphenylthioethyl bromide. However, condensation of *o*-hydroxybenzenethiol with excess of ethylene dibromide gave none of the required intermediate, only 1 : 2-bis-*o*-hydroxyphenylthioethane being isolated. The reaction was therefore carried out in one stage using equivalent quantities of the reactants.

o-Hydroxybenzenethiol (100 g., 1 mol.), ethylene dibromide (149 g., 1 mol.), and sodium ethoxide (120 g., slightly >2 mol.) were refluxed in ethanol (2·5 l.) for 24 hr. Most of the solvent was removed by distillation, and the residue added to water, made alkaline, and extracted with ether. The extract, dried and fractionated, yielded a little ethylene dibromide followed by *benz*-1 : 4-*oxathien* (24·2 g.), b. p. 90°/2 mm. (Found : C, 62·75, 62·7; H, 5·5, 5·2. C_8H_8OS requires C, 63·2; H, 5·3%). Acidifying the alkaline solution gave 1 : 2-bis-*o*-hydroxyphenylthioethane (25·5 g.).

Benz-1 : 4-oxathien (1 g.) and hydrogen peroxide (0·75 c.c.; 30%) were kept in acetic acid (25 c.c.) at room temperature for 5 days, then poured into excess of dilute aqueous alkali. The oily product crystallised after ether-extraction, and recrystallisation from light petroleum (b. p. 60—80°) gave *benz*-1 : 4-*oxathien* 4-*oxide* (0·75 g.) as plates, m. p. 85° (Found : C, 57·2; H, 4·5. $C_8H_8O_2S$ requires C, 57·15; H, 4·8%)

Benz-1 : 4-oxathien (1 g.) was suspended in a little water containing magnesium sulphate (2 g.), and 0·1N-potassium permanganate (450 c.c.) was slowly added at 70°. Decolorisation with sulphur dioxide and chloroform-extraction gave *benz*-1 : 4-*oxathien* 4-*dioxide* as needles (0·6 g.), m. p. 82° [from light petroleum (b. p. 60—80°)] (Found : C, 52·1; H, 4·5. $C_8H_8O_3S$ requires C, 52·2; H, 4·35%).

o-Hydroxybenzenethiol and Chloroacetic Acid.—To a solution of potassium hydroxide (30 g.) in water (300 c.c.) was added *o*-hydroxybenzenethiol (24 g.), followed by chloroacetic acid (24 g.). The solution was refluxed for 30 min., acidified, and evaporated to dryness. The product was extracted with ether, and the extract dried and evaporated. *o*-Hydroxyphenylthioacetic acid was obtained as an oil (35 g.) [Found : equiv. (by titration), 182, 178, 177, 176. Calc. for $C_8H_8O_3S$: equiv., 184]. On attempting to distil this compound at 3 mm., water was evolved and the resulting distillate (b. p. 128°) was insoluble in water or dilute alkali. Ring-closure had evidently occurred. The best yield was obtained by the following method :

Crude *o*-hydroxyphenylthioacetic acid (12 g.), obtained as above, was heated at 100°/3 mm. for 4 hr. Water and a solid distilled. The solid was identified by a mixed m. p. determination as chloroacetic acid (0·7 g.), doubtless present as an impurity in the starting material. 2-*Keto-benz*-1 : 4-*oxathien* (8·85 g.) was later collected at 128°/3 mm. (Found : C, 57·9; H, 3·7%; *M*, 162, 165. $C_8H_6O_2S$ requires C, 57·8; H, 3·6%; *M*, 166).

Crude *o*-hydroxyphenylthioacetic acid (10 g.), potassium hydroxide (11 g.), and chloroacetic acid (6 g.), refluxed in water (100 c.c.) for 3 hr. and then cooled and acidified, gave a pale brown solid (4·55 g.; m. p. 176—179°). Evaporation of the mother-liquor to dryness, ether-extraction, removal of the ether, and trituration of the residue with benzene gave only a trace of less pure product. Two recrystallisations from nitrobenzene gave o-*carboxymethylthiophenoxyacetic acid* (4·2 g.), m. p. 183° [Found : C, 49·3; H, 4·3%; equiv. (by titration), 124, 124. $C_{10}H_{10}O_5S$ requires C, 49·6; H, 4·1%; equiv., 121]. The compound was also obtained directly from *o*-hydroxybenzenethiol and 2 mols. of chloroacetic acid.

Esters of Hydroxyarenethiols.—Acetylation of *o*-hydroxybenzenethiol (6 g.) gave o-*acetylthiophenyl acetate* (7·85 g.), b. p. 130°/2 mm., 145°/5 mm., 154°/7 mm. (Found : C, 57·1; H, 4·9. $C_{10}H_{10}O_3S$ requires C, 57·15; H, 4·8%).

Similarly, 2-hydroxynaphthalene-1-thiol (10 g.) gave 1-*acetylthio*-2-*naphthyl acetate*, b. p. 196—198°/2 mm. The viscous oil solidified very slowly at 0°, and then recrystallised from light petroleum (b. p. 60—80°) as prisms (4·8 g.), m. p. 57° (Found : C, 64·5; H, 4·6. $C_{14}H_{12}O_3S$ requires C, 64·6; H, 4·6%).

Schotten–Baumann reactions gave o-*benzoylthiophenyl benzoate* (82%), needles, m. p. 68° (from ethanol) (Found : C, 71·6; H, 4·2. $C_{20}H_{14}O_3S$ requires C, 71·9; H, 4·2%), and o-(2 : 4-

dichlorobenzoylthio)phenyl **2** : **4**-*dichlorobenzoate*, prisms, m. p. 101—104° (from ethanol) (Found : C, 50·3, 51·3; H, 2·05, 2·0. $C_{20}H_{10}O_3SCl_4$ requires C, 50·85; H, 2·1%).

Refluxing *o*-hydroxybenzenethiol (1 mol.) and benzoyl chloride (1 mol.) in benzene until evolution of hydrogen chloride had almost ceased (40 hr.) gave a small yield of o-(*benzoylthio*)-*phenol*. After the benzene solution had been washed with N-sodium carbonate, the product was isolated by extraction with 2N-sodium hydroxide. Acidification gave a solid which recrystallised from light petroleum (b. p. 60—80°) as needles, m. p. 122°. The compound gave a greenish-brown colour with ferric chloride, but gave no colour change with alkaline nitroprusside solution, showing that it still contained the hydroxy-group, but no longer contained the thiol group (Found : C, 67·4; H, 4·7. $C_{13}H_{10}O_2S$ requires C, 67·8; H, 4·35%).

o-Hydroxybenzenethiol (2·5 g.) and phthaloyl chloride (4·9 g.) gave **5** : **8**-*diketo*-**2** : **3**-**6** : **7**-*dibenz*-**1**-*oxa*-**4**-*thia*cyclo*octa*-**2** : **6**-*diene* (VIII) (2·6 g.), a colourless powder of m. p. *ca.* 72° (decomp.) [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 65·65; H, 3·45. $C_{14}H_8O_3S$ requires C, 65·6; H, 3·1%).

The authors are grateful to Mr. E. L. Collier for experimental assistance, and to Mrs. F. Weston and Miss C. Coleman for the semi-micro-analyses.

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310. *The Selective Absorption of Optical Antipodes by Proteins. Part II.**

By WILLIAM BRADLEY and GERALD C. EASTY.

The study of the selective absorption of (+)-mandelic acid on wool (*J.*, 1951, 499) has been extended to mandelic acid derivatives. The relation between the amounts of acid absorbed and resolved has been determined, and, in addition, the stability of the wool protein–mandelic acid complexes. These results, together with parallel observations on the stability of the salts of mandelic acid with L-arginine and L-lysine, suggest that the resolution of mandelic acid on wool occurs at the L-arginine and L-lysine residues, and mainly, if not entirely, in the crystalline regions of the fibre.

IN a previous communication * it was shown that wool and casein selectively absorb (+)-mandelic acid from an aqueous solution of (±)-mandelic acid at room temperature. The resolution was attributed to the formation of salts by the union of wool-protein with the (+)- and the (−)-acid, that with the (+)-acid being the more abundant. The absorption of mandelic acid by wool has now been examined more closely, and it has been found that under conditions similar to those described in Part I equilibrium is reached after 5—6 days at 31·3°, and that three-quarters of the acid ultimately bound combines within 4 min. of contact. At equilibrium the excess of (+)- over (−)-acid combined amounts to 3·5%; after 4 min. it is 2·1%. Resolution of the acid thus occurs from the beginning of the absorption. After the first 4 min. the increase in the excess of (+)-acid combined is proportional to the increase in the total acid combined.

When brought into equilibrium with aqueous (±)-mandelic acid at pH 2·5 and 31·3°, 1 kg. of wool combines with 0·45 mole of acid. The result accords with that reported for hydrochloric acid (0·4 mole) and chloroacetic acid (0·44 mole) at 0° and pH 2·5 (Steinhardt, Fugitt, and Harris, *J. Res. Nat. Bur. Stand.*, 1940, **25**, 519; 1941, **26**, 293), and with the same authors' observation that the amount of hydrochloric acid combined is almost independent of temperature between 0° and 50°.

The absorption of mandelic acid by wool is not accompanied by hydrolysis of the wool-protein or by structural changes other than those which accompany salt-formation. Wool which had been brought into equilibrium with mandelic acid during 5 days, then freed of acid, again equilibrated with mandelic acid under the same conditions, and finally rendered

* The previous paper, with the same general title (*J.*, 1951, 499), is now regarded as Part I of the series.

acid-free, showed the same behaviour as the original wool when immersed in aqueous (±)-mandelic acid. Further, the total absorption and resolution of mandelic acid remained unaltered when the period of contact was increased from 5 to 15 days.

The protein–acid complex prepared by immersing wool in aqueous (±)-mandelic acid remained unchanged in composition when transferred to a second portion of the same solution. The complex prepared from wool and an aqueous solution of pure (−)-mandelic acid, however, changed in composition when transferred to an aqueous solution of the (±)-acid, some of the combined (−)-acid being replaced by the (+)-form. The rate of replacement was low, only 3% of the combined (−)-acid being replaced in 4 days at 15°.

It is generally considered that the acid-binding capacity of wool-protein is due mainly to the presence of arginine and lysine, and in lesser degree histidine, residues. For this reason we have investigated the union of L-arginine and L-lysine with mandelic acid. Each of these combines with mandelic acid and each forms a product containing more of the (+)- than of the (−)-acid. L-Arginine forms a white crystalline salt, $C_6H_{14}O_2N_4,2C_8H_8O_3$. When crystallised from a solution of the components in absolute alcohol, or in a mixture of equal volumes of alcohol and water, the salt contains the (+)- and the (−)-form of mandelic acid in the ratio 1·02 : 1·00. The same salt is formed when a solution of (±)-mandelic acid in alcohol is added to solid L-arginine. In these circumstances the yield of salt is smaller, the degree of resolution is higher (20—30% instead of 2—3%), and the occurrence of resolution coincides with the separation of the salt on the surface of the L-arginine.

The salt containing approximately 2% more of the (+)- than the (−)-acid remained unaltered in composition after 8 days' contact with an alcoholic solution of the (±)-acid at 15°. The salt prepared analogously from pure (−)-mandelic acid, however, altered in composition in contact with the (±)-acid, a portion of the (−)-acid being replaced by the (±)-form from the solution. A feature of the replacement reaction was the low rate at which it occurred; only 4% of the combined acid was replaced in 15 days. The result indicates that the high degrees of resolution observed when alcoholic (±)-mandelic acid is brought into contact with solid L-arginine arise from a difference in the rates of the initial reaction of (+)- and (−)-mandelic acid with L-arginine, and not from subsequent replacement of the (−)-acid by the (+)-form. The close similarity in the behaviour of wool and L-arginine towards (±)-mandelic acid is also evident.

The replacement of (−)- by (+)-mandelic acid in combination with wool-protein is interesting in relation to other phenomena. Elöd (*Trans. Faraday Soc.*, 1933, **29**, 327) found that wool immersed in aqueous hydrochloric acid containing the disodium salt of 1-α-naphthylazo-2-naphthol-3 : 6-disulphonic acid combined first with hydrogen and chloride ions, and that the latter were subsequently replaced by anions of the dye. The mandelic acid experiment shows that interchange of anions can take place on wool independently of a difference in composition between the anions.

It is generally held that wool consists of amorphous and crystalline forms of a protein, the amorphous regions being the more accessible. All parts of the fibre are ultimately reached by acids of small molecular dimensions (Astbury and Dawson, *J. Soc. Dyers and Col.*, 1938, **54**, 6).

The present results, together with parallel studies on the desorption of mandelic acid from wool, suggest the following sequence of events. First, mandelic acid is taken up rapidly by the readily accessible amorphous regions of wool-protein and then more slowly by the crystalline portions. The second phase is characterised by the constancy of the ratio, $\frac{\text{excess of (+)- over (−)-acid absorbed}}{\text{total acid absorbed}}$, which suggests that the composition of the wool-protein concerned is uniform.

There was no evidence of resolution when degummed silk was brought into contact with aqueous (±)-mandelic acid. The result could be due to the smaller proportion of basic amino-acids in silk protein, but another possibility is that resolution occurs most readily in the crystalline regions of proteins, and it is known that the more highly orientated regions of silk do not contain either L-lysine or L-arginine (Trogus and Hess, *Biochem. Z.*, 1933, **260**, 376; Coleman and Howitt, *Nature*, 1945, **155**, 78).

We have extended the experiments with mandelic acid to several of its substitution

products including *o*-, *m*-, and *p*-nitro-, *p*-methoxy-, and *o*-ethoxy-mandelic acid. Each of these was absorbed and resolved. In contrast *m*-(*p*-hydroxyphenylazo)mandelic acid was not resolved. In other experiments it has been shown that mandelic acid is resolved by L-lysine but not by L-histidine or L-glutamic acid.

Experimental

Combination of L-Arginine with (±)-Mandelic Acid.—(*a*) L-Arginine (0·992 g., $[\alpha]_D$ +12·1° in H_2O) was dissolved in a warm solution of (±)-mandelic acid (2·040 g.; m. p. 118·5—119°) in alcohol (30 c.c.). After several days at the toom temperature the *salt* separated as needles; these were washed with ethyl alcohol [(yield, 1·065 g.; m. p. 156—157°) (Found: C, 54·8; H, 6·4. $C_6H_{14}O_2N_4,2C_8H_8O_3$ requires C, 55·2; H, 6·3%), and a portion (0·794 g.) was dissolved in N-hydrochloric acid. The solution, extracted with ether, gave 0·474 g. of mandelic acid [α_D + 0·04° for a solution (17·5 c.c.) in alcohol]. (Measurements of optical activity were made as described in Part I.) The alcoholic mother-liquor, when evaporated to dryness, afforded a residue, and this was digested with ether. The extract afforded 0·294 g. of mandelic acid with α_D −0·02°. The ether-insoluble residue (1·520 g.) dissolved in hydrochloric acid; the solution, extracted with ether, gave 0·910 g. of mandelic acid, α_D −0·03°. Both the needles and the ether-insoluble residue from the alcoholic mother-liquor contained 60·0% of mandelic acid as found by the ether-extraction procedure (Calc. for $C_6H_{14}O_2N_4,2C_8H_8O_3$: $C_8H_8O_3$, 63·6%). Similar results were obtained when 50% aqueous alcohol was substituted for alcohol.

(*b*) A solution (20·0 c.c.) of (±)-mandelic acid (1·500 g.) in alcohol was added to powdered anhydrous L-arginine (0·750 g.). At intervals 17·5 c.c. of the solution were removed, examined polarimetrically, and returned (see Table 1). The change in rotation at 64 hours coincided with

Table 1.

Time (hr.)	23	64	220	238
α	+0·18°	−1·01°	−2·51°	−2·53°

the separation of crystals on the surface of the L-arginine. After 238 hr. the suspension was filtered and the crystals (1·301 g.) were collected. They contained 0·635 g. of mandelic acid (Found: C, 62·7; H, 4·9; N, 0. Calc. for $C_8H_8O_3$: C, 63·2; H, 5·3%), α_D +2·47° as a solution (17·5 c.c.) in alcohol. The filtrate, evaporated to dryness, gave a residue and this was digested with ether. The soluble fraction was mandelic acid (0·794 g.), α_D −2·46° as a solution (17·5 c.c.) in alcohol. The insoluble portion (0·076 g.) was a salt containing 0·045 g. of mandelic acid (59%) and having α_D −0·15° as a solution (17·5 c.c.) in alcohol.

The (+)-form of mandelic acid combined preferentially in similar experiments with L-lysine instead of L-arginine, but no resolution was observed when the solid phase was L-glutamic acid, L-asparagine, L-tyrosine, L-alanine, or L-histidine.

L-Arginine Dimandelate and (±)-Mandelic Acid.—L-Arginine dimandelate was prepared from the components in alcohol (0·1954 g. of the salt gave 0·1140 g. mandelic acid having $[\alpha]_D$ +3·0°). The finely powdered salt (0·4054 g.) was kept in a stoppered flask for 8 days at 15° with a solution of (±)-mandelic acid in alcohol (20 c.c.). The undissolved crystals were collected and washed with ether (yield, 0·392 g.); they afforded 0·227 g. of mandelic acid, $[\alpha]_D$ +3·0°. The filtrate contained only inactive mandelic acid (0·4802 g.).

L-Arginine (−)-Mandelate and (±)-Mandelic Acid.—The powdered salt prepared from (−)-mandelic acid, $[\alpha]_D$ −160°, was repeatedly extracted with ether and then suspended for 24 hours in more dry ether. The medium remained optically inactive. The purified salt (0·3868 g.) was suspended at 15° in alcohol (20 c.c.) containing (±)-mandelic acid (0·4840 g.). At intervals 17·5 c.c. of the solution were removed, examined polarimetrically (see Table 2) and

Table 2.

Time (hr.)	45	24	73
α_D	−0·25°	−0·30°	−0·33°

then returned. After 8 days the salt was collected and washed with a small volume of ether. The filtrate and washings were concentrated, filtered, and finally evaporated to dryness. The residue was mandelic acid (0·421 g.; m. p. 118·5°; $[\alpha]_D$ −13°). The mandelic acid extracted from the salt had become correspondingly less lævorotatory ($[\alpha]_D$ −132°).

Replacement of (−)- by (+)-Mandelic Acid on Wool.—Wool fibres (50 g.; purified as described in Part I) were kept for 6 days at the room temperature in water (1250 c.c.) containing (−)-

mandelic acid (10 g.; $[\alpha]_D$ −160°). The wool was then removed, squeezed as free as possible from the medium, and immersed immediately in water (1250 c.c.) containing (±)-mandelic acid (10 g.). After 30 min. the wool was removed, squeezed, and finally kept for 4 days in a similar solution of (±)-mandelic acid. The solution then afforded 9·88 g. of mandelic acid, $[\alpha]_D$ −5·4°.

Relation between the Rates of Absorption and Resolution of Mandelic Acid on Wool.—Wool fibres were extracted (Soxhlet) with absolute alcohol for 24 hr., then with ether for the same period, and finally with alcohol for 8 hr. After being washed with water, they were dried in air and stored over anhydrous calcium chloride *in vacuo*.

Purified wool (30·0 g.) was immersed in distilled water at 31·3° and, when thoroughly wetted, was squeezed and then transferred to a solution of (±)-mandelic acid (5·000 g.) in water (500 c.c.) at 31·3°. At intervals the wool was collected, pressed in a coarse-mesh sintered-glass funnel, and thoroughly squeezed. The adsorbed mandelic acid was removed by treatment with dilute aqueous ammonia, and the weights and rotations of the absorbed and unabsorbed acid were determined. The time of immersion of the wetted wool in the aqueous acid was taken as zero, and the period of immersion as the time which elapsed until the wool was removed and one-half of the acid solution had been filtered. The filtration stage occupied 10—15 sec. in all. Each result recorded in Table 3 is the mean of several.

TABLE 3.

Time (sec.)	Unabsorbed (g.)	α_D	Mandelic acid absorbed (g.)	α_D	Total accounted for (g)	Mandelic acid (%) absorbed *	Mandelic acid (%) resolved *
30	3·667	−0·05°	1·017	+0·06°	4·684	49·9	25·0
75	3·447	−0·08	1·309	+0·09	4·756	64·3	37·5
105	3·321	−0·10	1·401	+0·10	4·722	68·8	41·7
225	3·206	−0·14	1·503	+0·14	4·709	73·8	58·3
420	3·172	−0·15	1·565	+0·15	4·717	76·8	62·5
660	3·012	−0·15	1·709	+0·16	4·721	83·9	66·7
950	2·962	−0·16	1·742	+0·17	4·704	85·5	70·8
1320	2·841	−0·17	1·871	+0·18	4·712	91·8	75·0
1800	2·802	−0·18	1·917	+0·19	4·712	94·8	79·5
5 days	2·679	−0·23	1·994	+0·24	4·673	100	100
6 days	2·651	−0·24	2·080	+0·24	4·731	100	100

* After 6 days.

TABLE 4.

Duration of contact (days)	5	5	10	10	15	15
Unabsorbed acid, g.	2·719	2·784	2·741	2·754	2·825	2·721
,, α_D	−0·22°	−0·23°	−0·24°	−0·23°	−0·23°	−0·24°

TABLE 5.

Contact (sec.)	Acid desorbed (g.)	α_D	Acid combined with wool (g.)	α_D	Acid desorbed as % of acid desorbed after 15 days
55	0·406	0·00°	1·627	+0·24°	55
90	0·485	−0·01	1·542	+0·24	66
180	0·551	−0·01	1·446	+0·25	75
420	0·676	−0·01	1·340	+0·24	92
670	0·718	−0·02	1·284	+0·26	98
5 days	0·761	−0·01	1·249	+0·24	
10 ,,	0·702	−0·01	1·273	+0·23	100
15 ,,	0·741	−0·01	1·260	+0·26	

Desorption of Mandelic Acid from Wool.—(*a*) Wool (30 g.) was brought into contact with a solution of mandelic acid (5 g.) in water (600 c.c.) at room temperature. The results in Table 4 were obtained. The wool containing the absorbed acid was immersed in water (600 c.c.) for a time. The solution was then filtered and the amount of acid remaining on the wool and the quantity desorbed were determined, together with the rotations of the two fractions (see Table 5).

(*b*) Wool (30 g., dry wt.) was brought into equilibrium with mandelic acid (5 g.) in water (600 c.c.) at room temperature; 2·525 g. of acid remained unabsorbed (α_D −0·26°). The wool was withdrawn, immersed in water (600 c.c.), and withdrawn after a time, and the immersion and removal repeated with fresh water (600 c.c.) at each stage. Results are in Table 6. 0·465 g. of acid remained absorbed (α_D +0·16°).

Effect of Previous Treatment with Mandelic Acid on the Selective Absorption of Mandelic Acid by Wool.—Wool (30 g., dry wt.) was immersed in a solution of mandelic acid (5 g.) in water (600 c.c.) for 5 days at the room temperature. The resulting solution was filtered and the absorbed acid removed from the wool by immersion in 1·5% aqueous ammonia (400 c.c.) for 10 min., filtration, reimmersion for the same time in 300 c.c. of a similar solution, and finally washing in

TABLE 6.

Desorption (hr.)	Acid desorbed (g.)	α_D	Total acid desorbed (% of total acid absorbed)
0·5	0·834	−0·02°	36
0·5	0·421	0·00	54
0·5	0·241	0·02	64
18·0	0·379	0·07	80

TABLE 7.

Cycle	Acid absorbed g.	α_D	Acid unabsorbed g.	α_D
First	2·394	0·25°	2·543	−0·25°
Second	2·382	0·24	2·522	−0·25
Third	2·351	0·25	2·574	−0·25

running water for 12 hours. The treated wool was brought into equilibrium with aqueous mandelic acid of the inital concentration, the system was analysed, and the sorption and desorption were repeated several times with the same sample of wool. The results shown in Table 7 were obtained. The rates of absorption and resolution of mandelic acid on the original sample of wool were compared with the corresponding rates on wool which had completed one cycle of sorption and desorption : for results see Table 8.

TABLE 8.

Contact (min.)	(g.)	Acid absorbed % of equilibrium amount	α_D	% of equilibrium value	Acid unabsorbed (g.)	α_D
Original wool.						
1	1·049	44	0·05°	19	3·851	−0·05°
3	1·644	68	0·10	38	3·270	−0·10
10	1·936	80	0·17	65	2·941	−0·18
5 days	2·418	100	0·26	100		
Mandelic acid-treated wool.						
1	1·025	43	0·05	20	3·805	−0·05
2	1·373	58	0·08	32	3·442	−0·08
5	1·730	73	0·12	48	3·191	−0·11
13	2·147	90	0·18	72	2·724	−0·18
5 days	2·366	100	0·25	100	2·532	−0·25

Selective Absorption of Mandelic Acid Derivatives.—The absorption of substituted mandelic acids, prepared by known methods, on wool was studied by the following method. 30 g. of dry wool were left in contact with an amount of acid approx. equivalent to 5 g. of mandelic acid, in a mixture of water (400 c.c.) and ethyl alcohol (300 c.c.), for 5 days at the room temperature. The solutions were evaporated at the room temperature under reduced pressure (but at 20—30° for the *o*-ethoxy-acid). Low-temperature evaporation was especially necessary with *o*-nitromandelic acid which developed a red colour when heated. Results are in Table 9.

TABLE 9

R in $C_6H_4R{\cdot}CH(OH){\cdot}CO_2H$	Wt. of acid (g.)	Acid absorbed g.	α_D	Acid unabsorbed g.	α_D
H	5·0	2·194	0·29°	2·707	−0·28°
o-NO_2	6·6	2·978	0·35	3·524	−0·32
m-NO_2	6·6	2·899	0·17	3·175	−0·18
p-NO_2	6·6	2·760	0·17	3·648	−0·17
p-OMe	6·0	2·471	0·24	3·310	−0·25
o-OEt	6·45	2·315	0·23	3·976	−0·22
p-OH (as monohydrate)	5·09	2·547	0·20	2·354	−0·22

m-(p-*Hydroxyphenylazo*)*mandelic Acid.*—Wool (50 g., dry wt.) was treated with *m*-(*p*-hydroxyphenylazo)mandelic acid (6·66 g.) (Brode and Adams, *J. Amer. Chem. Soc.*, 1926, **48**, 2202) in a mixture of water (500 c.c.) and ethyl alcohol (300 c.c.) for 5 days at room temperature.

The unabsorbed acid (1·277 g.) was recovered by evaporation at 30—40° under reduced pressure, and the absorbed acid (4·4 g.) by treatment with hot dilute aqueous ammonia. Solutions of both fractions were too deeply coloured for accurate measurement of optical rotation. Each was reduced, therefore, with sodium dithionite, but in neither case did the observed rotation of the resulting pale yellow solution exceed the limit of experimental error.

Absorption of Mandelic Acid by Silk Fibroin.—Degummed, unweighted, natural silk was extracted (Soxhlet) with alcohol and then ether, and washed with water. The silk (115 g., dry wt.) was then left in a solution of (±)-mandelic acid (10 g.) in water (800 c.c.) for 5 days at room temperature. The weight of acid absorbed was 4·885 g., and of acid unabsorbed 4·768 g. Both fractions were optically inactive.

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311. *Syntheses in the Morphine Series. Part IV.* The Synthesis of N-Methylmorphinan.*

By DAVID GINSBURG and RAPHAEL PAPPO.

Various methods for formation of the tetracyclic skeletal structure present in morphine from 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenanthrene compounds previously described (*J.*, 1951, 938) have been investigated. *N*-Methylmorphinan has been prepared by one of these routes.

THE present communication describes attempts to join $C_{(10)}$ and $C_{(12)}$ of the octahydrophenanthrene derivatives (*e.g.*, I*a* or *b*) described in Part III * by the "ethanamine" bridge, $-CH_2{\cdot}CH_2{\cdot}NMe-$, and thus to approach more closely to the morphine structure.

Formally, three routes are open: (*a*) introduction of an amino- or potential amino-group at $C_{(10)}$ and of an appropriate two-carbon chain at $C_{(12)}$, and junction of the two: $C_{(10)}{-}N + C{-}C{-}C_{12} \longrightarrow C_{(10)}{-}N{-}C{-}C{-}C_{(12)}$; (*b*) alkylation of $C_{(12)}$ by a substituent which can be converted into a two-carbon chain carrying in the β-position an amino- or potential amino-group, and introduction at $C_{(10)}$ of a halogen atom or another substituent which will react with the amino-group: $C_{(12)}{-}C{-}C{-}N + C_{(10)}{-}X \longrightarrow C_{(12)}{-}C{-}C{-}N{-}C_{(10)}$; and (*c*) introduction at $C_{(10)}$ of a substituted amino-group, the substituent being suitable for intramolecular alkalylation at $C_{(12)}$: $C_{(10)}{-}N{-}C{-}C{-}X + C_{(12)} \longrightarrow C_{(10)}{-}N{-}C{-}C{-}C_{(12)}$. So far, route (*c*) has yielded a product containing the tetracyclic system present in the morphine alkaloids. The tetracyclic nature of the cyclisation product has been proved by its conversion in a series of simple transformations into *N*-methylmorphinan (Grewe and Mondon, *Ber.*, 1948, **81**, 279).

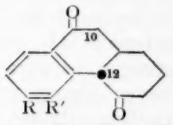
(*a*, 1) *Introduction of an Amino-group at* $C_{(10)}$.—Michael condensation of 2-aryl*cyclo*hex-2-enones with methyl nitroacetate yielded methyl 2-aryl-3-keto*cyclo*hexyl-α-nitroacetates (Part III). These were converted by high-pressure reduction in the presence of Raney nickel into the corresponding α-amino-acetates, and these were hydrolysed to the α-amino-acids (II*a* and *b*). The more readily available unmethoxylated substances were used throughout as models in developing the synthetic procedures.

The phthalimido-acid (III) formed from (II*a*) was cyclised by means of sulphuric acid to *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketo-10-phthalimidophenanthrene (IV). This cyclisation was possible due to the removal of the basic properties of the amino-group through the phthaloyl radical (cf. Sheehan and Frank, *J. Amer. Chem. Soc.*, 1949, **71**, 1856).

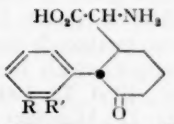
Support for the structure of (IV) was obtained through its synthesis by another route in which it was obtained in higher overall yield. The 4-ethylene glycol ketal of (I*b*) was

* Part III, *J.*, 1951, 938.

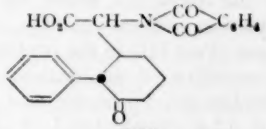
converted by means of amyl nitrite in the presence of sodium ethoxide into the 10-oximino-derivative (V), hydrogenated in the presence of 10% palladium–carbon to the 10-amino-compound (VI*a*). Hydrolysis of the 4-ethylene glycol ketal grouping in the derived 10-phthalimido-derivative gave a substance identical in melting point, mixed melting point, and infra-red absorption with (IV). Alternatively, the 10-oximino-compound could be



(I*a*; R = R′ = OMe)
(I*b*; R = R′ = H)



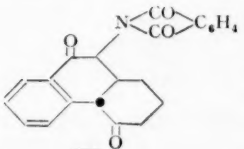
(II*a*; R = R′ = H)
(II*b*; R = R′ = OMe)



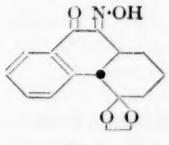
(III)

reduced catalytically in the presence of hydrochloric acid to yield the hydrochloride of the 10-amino-4 : 9-diketo-compound (VII*a*). The free base on treatment with phthalic anhydride again yielded (IV). The stereochemistry of (VII*a*) is discussed below.

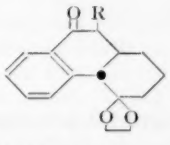
Michael condensation of 2-phenyl*cyclo*hex-2-enone with ethyl or benzyl malonate on the one hand, and with methyl nitroacetate on the other, yields adducts having the *trans*-configuration (Pappo and Ginsburg, *Bull. Res. Council Israel*, 1951, **1**, No. 3, 121). That the *trans*-adduct is obtained with ethyl or benzyl malonate has been shown by conversion of the adduct into the known *trans*-2-phenyl*cyclo*hexylacetic acid (Part III, *loc. cit.*; Bachmann and Fornefeld, *J. Amer. Chem. Soc.*, 1950, **72**, 5529). That the *trans*-adduct is formed also with methyl nitroacetate (and by analogy, presumably with other donors in the Michael condensation) has been shown by the synthesis of (IV) by the two routes described. In the Experimental section an improved procedure is given for the preparation of malonate or cyanoacetate adducts in the Michael condensation. Benzyl malonate or cyanoacetate, used in place of the ethyl esters, affords more simply isolated, pure intermediates and increases the overall yield of the final products. The use of benzyl esters (cf. Bowman, *J.*, 1950, 325) was of particular importance in condensations in the dimethoxyphenyl series because acid hydrolysis of the ethyl malonate or ethyl cyanoacetate adduct in this case yielded an intractable mixture which was not further investigated. Hydrogenolysis of the benzyl ester adducts permits one to avoid the use of intermediate 4-ethylene glycol ketal derivatives. The method has proved to be of wide scope and is useful whenever basic hydrolysis of products of Michael condensation is not possible.



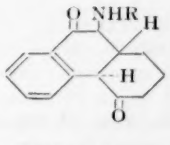
(IV)



(V)



(VI*a*; R = NH_2)
(VI*b*; R = CO·CO_2Et)
(VI*c*; R = CO_2Et)



(VII*a*; R = H)
(VII*b*; R = CO·CH_2·Halogen)
(VII*c*; R = CO·CH_2·OAc)

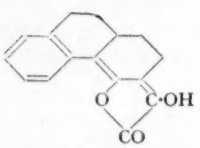
(*a*, 2) *Introduction of an Ester Group at* $C_{(10)}$.—An ester group could be introduced at $C_{(10)}$ indirectly by treatment of a compound having a carbonyl group at $C_{(9)}$ with ethyl oxalate. Decarbonylation in the presence of powdered soft glass of the 10-ethoxalyl derivative (cf. Snyder, Brooks, and Shapiro, *Org. Synth.*, Coll. Vol. II, p. 531) gave smoothly the corresponding carbethoxy-compound. The ester group is convertible into an amino-group by any of the known procedures but this approach was abandoned in favour of the simpler route (*a*, 1).

Glyoxylation at $C_{(10)}$ of the 4-ethylene glycol ketal of (I*a* or *b*) proceeded smoothly in high yield when sodium hydride was used as the condensing agent, but in extremely poor yield in the presence of sodium methoxide or ethoxide. A similar effect has been observed in the acylation of ethyl *iso*valerate (Swamer and Hauser, *J. Amer. Chem. Soc.*, 1950, **72**,

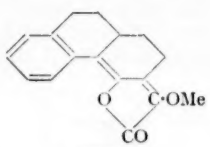
1352). In both cases the carbon atom in the β-position with respect to the carbonyl (or ester) group is highly substituted. This is probably the reason for the poor results encountered in the sodium methoxide-catalysed glyoxylation, as α-tetralones are known to condense smoothly under similar conditions with alkyl oxalates (Bachmann, Cole, and Wilds, *ibid.*, 1940, **62**, 824).

In the diketones, when the $C_{(1)}$-carbonyl group is free, sodium methoxide-catalysed glyoxylation occurs at $C_{(3)}$. *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-Octahydro-4-ketophenanthrene (Part III) in the presence of sodium methoxide yielded a lactone (VIII), owing to the possibility of enolisation in the product which bears a hydrogen atom at $C_{(12)}$ (cf. Bachmann, Fujimoto, and Wick, *ibid.*, 1950, **72**, 1995). However, glyoxylation at $C_{(3)}$ of 12-2′-cyanoethyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4-ketophenanthrene (XI*a*) (see below), in which the $C_{(12)}$-atom is quaternary, yielded a normal glyoxylate. The difference in reactivity between the carbonyl groups in (I*b*) has been observed before (Part III). It is, therefore, not surprising that glyoxylation of (I*b*) with sodium methoxide as catalyst yielded a *mono*glyoxylate at $C_{(3)}$ which could not be isolated but formed the lactone (X) in high yield.

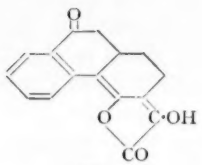
(*a*, 3) *Alkylation at* $C_{(12)}$.—2-Phenyl*cyclo*hexanone and 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4-ketophenanthrene were used as model substances for the study of the introduction of substituents at the tertiary carbon atom. Newman and Farbman (*ibid.*, 1944, **66**, 1550) have shown that 2-phenyl*cyclo*hexanone can be alkylated at the tertiary carbon atom (C_2) by means of methyl iodide in the presence of sodamide, and Newman and Magerlein (*ibid.*, 1947, **69**, 942) have introduced a 2-ethoxyethyl group at $C_{(2)}$ by means of 2-ethoxyethylmethanesulphonate and sodamide (see, also, Boekelheide, *ibid.*, 1950, **72**, 712). It has now been found that, equally, the 2-benzyloxyethyl group can be introduced at $C_{(2)}$ by means of 2-benzyloxyethylmethanesulphonate and sodamide. This modification is useful in view of the potential possibility of hydrogenolysis of the benzyloxy-group, a point which assumes major importance in the methoxylated compounds more closely related to morphine: the conditions under which an ethyl ether group in the alkyl side chain would be cleaved will also demethylate the aromatic methoxyl groups (Horning and Schock, *ibid.*, 1949, **71**, 1359).



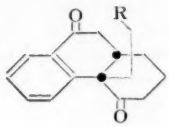
(VIII)



(IX)



(X)



(XI*a*; R = CN)
(XI*b*; R = CO_2H)
(XI*c*; R = $CO{\cdot}NH_2$)

In the case of the octahydro-4-ketophenanthrene, however, the angular alkylation was not so satisfactory. The ratio of alkylation at $C_{(12)}$ and at $C_{(3)}$ varied with the nature of the alkylating reagent; several examples are given in the Experimental section. As it became further apparent that 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4-ketophenanthrene and its 5 : 6-dimethoxy-derivative and more complex analogues behave differently under identical conditions, the study of the $C_{(12)}$-alkylation of model compounds was abandoned in favour of procedures of more immediate value for further synthetical elaboration. The dissimilarity in the behaviour of the corresponding phenyl and dimethoxyphenyl analogues under a given set of experimental conditions has been observed previously (Horning and Finelli, *ibid.*, 1951, **73**, 3741). The same is true for certain phenyl and trimethoxyphenyl analogues used by a number of investigators in the elaboration of the colchicine structure (Ginsburg and Pappo, *J. Amer. Chem. Soc.*, in the press; Dr. Henry Rapoport, personal communication).

(*b*) *Cyanoethylation at* $C_{(12)}$.—Treatment of (I*b*) with acrylonitrile in the presence of benzyltrimethylammonium hydroxide (Triton B) (cf. Bruson, "Cyanoethylation," "Organic Reactions," Vol. V, Wiley, New York 1949, pp. 99—103) yielded as the major

product a mono-2-cyanoethyl derivative at $C_{(12)}$ (XI*a*). The possibility of cyanoethylations having occurred at $C_{(3)}$ or $C_{(10)}$ was excluded by the observation that the reaction product yielded crystalline dibenzylidene and dipiperonylidene derivatives in high yield. Accordingly, the 4-ethylene glycol ketal of (I*b*) was unchanged when cyanoethylation was attempted under the conditions used for cyanoethylation of (I*b*). (XI*a*) was hydrolysed to the corresponding acid (XI*b*).

It was found also that the *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4-ketophenanthrene with acrylonitrile in the presence of Triton B yielded mainly the *cis*-12-2′-cyanoethyl derivative (XII*a*), and a small quantity of bis-2-cyanoethyl product. That cyanoethylation occurred at $C_{(12)}$ was confirmed by the preparation of a benzylidene derivative and of a glyoxylate. Hydrolysis of (XII*a*) gave the acid (XII*b*), identical with a specimen obtained by catalytic hydrogenolysis of (XI*b*).

Both the structure and the steric configuration of (XI*a*) and (XII*a*) could be demonstrated directly by a simple series of transformations. *cis*-12-2′-Carboxyethyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4-ketophenanthrene (XII*b*) was reduced by the Huang-Minlon procedure (*ibid.*, 1946, **68**, 2487) to *cis*-12-2′-carboxyethyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenanthrene (XIII*a*). This acid was converted into the azide, which by a Curtius rearrangement gave *cis*-12-2′-aminoethyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenanthrene (XIII*b*). Methylation of the primary amine with formaldehyde–formic acid yielded *cis*-12-2′-dimethylaminoethyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenanthrene (XIII*c*). The structure of this product was shown by the fact that it did not depress the melting point of a specimen of " dihydrodes-base " obtained from *N*-methylmorphinan (*cis*-junction) (Grewe and Mondon, *loc. cit.*) and kindly supplied by Professor Rudolf Grewe, but gave a large melting-point depression with the " dihydrodes-base " obtained from *N*-methyl*iso*morphinan (*trans*-junction) (Gates, Woodward, Newhall, and Künzli, *J. Amer. Chem. Soc.*, 1950, **72**, 1141) and kindly supplied by Dr. Marshall Gates.

(XII*a*; R = CN)
(XII*b*; R = CO_2H)

(XIII*a*; R = CO_2H)
(XIII*b*; R = NH_2)
(XIII*c*; R = NMe_2)

(XIV*a*) (XIV*b*)

The formation of the *cis*-12-2′-cyanoethyl derivative (XII*a*) from *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4-ketophenanthrene may be explained by the fact that, as is well known, the active species of the donor in the Michael condensation is the hybrid of the enolate ion (XIV*a*) and the carbanion (XIV*b*), in either of which the steric configuration previously existing no longer obtains. Only the *cis*-12-2′-cyanoethyl product could be isolated from the reaction mixture, together with a small amount of bis-2-cyanoethyl product.

It is evident that in this case the approach of the 2-cyanoethyl moiety from the top of the molecule is hindered, so that a *cis*-relation between the hydrogen atom and the 2-cyanoethyl group is built up at the ring junction. The subtle effect exerted by the neighbouring polar groups in the present system is more pronounced than in the analogous case of methylation of 2-benzylidene-*trans*-1-decalone (Johnson, *ibid.*, 1943, **65**, 1317) or of 2-methylanilinomethylene-1-decalone (Birch and Robinson, *J.*, 1944, 501). In the last two examples mixtures of *cis*- and *trans*-9-methyl derivatives were obtained, although the *cis*-isomer predominated in the ratio of 3 : 1 (see Bergmann, Ginsburg, and Pappo, " The Michael Condensation," " Organic Reactions," in the press).

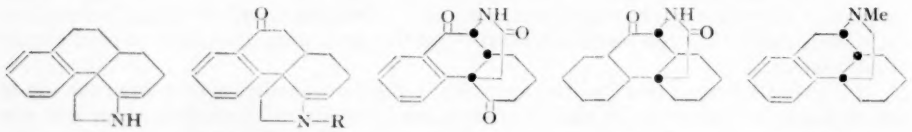
A compound such as (I*a* or *b*) is, however, of greater interest for further synthetic work and its mono-2-cyanoethyl derivative (XI*a*) was therefore investigated. The acid (XI*b*) was converted into its azide or hydrazide which were degraded by modifications of the Curtius rearrangement. In each case, the product was not the free primary amine but

the tetracyclic compound (XVI*a*) (cf. Bachmann and Fornefeld, *J. Amer. Chem. Soc.*, **1951**, **73**, 51). The position of the double bond in (XVI*a*) was deduced from the infra-red absorption spectrum which showed bands at 6·06 (C=C double bond), 3·10 (NH group), and 5·95 μ (carbonyl group conjugated with the aromatic ring). With methyl sulphate, (XVI*a*) gave the *N*-methyl product (XVI*b*). This ene-amine is being studied in order to determine whether it can be utilised for further synthetic elaboration to form *N*-methylmorphinan. The pyrrolidino-compound (XV) was similarly prepared from the octahydro-4-ketophenanthrene.

The amide (XI*c*) formed from the acid chloride of (XI*b*) was treated with bromine under the conditions of the Hofmann degradation in the hope that the amine formed would be further brominated and a tetracyclic product formed in analogy with the formation of cinchoninone from *N*-bromocinchonicine (Rabe, *Ber.*, 1911, **44**, 2088). This hope has not as yet been realised.

(*c*) *Intramolecular Cyclisation of Substituted* 10-*Amino-derivatives.*—The 4-ethylene glycol ketal (VI*a*) of 10-amino-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketophenanthrene was treated with halogenoacetyl chlorides (halogen = Cl, Br, or I). The 4-ethylene glycol ketals of the halogeno-amides (VII*b*) were obtained. Intramolecular alkylation of the free halogeno-amides (VII*b*) at $C_{(12)}$, in presence of various alkaline condensing agents, was unsuccessful: the chloro- and the bromo-amide were recovered unchanged; the iodo-amide apparently underwent, in part, double decomposition with sodamide to give sodium iodide and a basic amino-amide. Bromination of the bromo-amide at $C_{(12)}$, followed by attempted debromination of the resulting product with activated zinc in order to form a tetracyclic system, also failed.

The 10-amino-compound (VII*a*) and acetylglycolloyl chloride in the presence of pyridine gave the acetoxy-amide (VII*c*) in high yield. When preparation of the 4-ethylene glycol ketal of this amide was attempted, the compound unexpectedly lost the elements of acetic acid and the *cis*-diketo-lactam (XVII) was formed and isolated as its 4-ethylene glycol ketal. The infra-red spectrum of this compound was very similar to that reported by Gates *et al.* (*loc. cit.*) for the corresponding *trans*-lactam with one carbonyl group less: it showed bands at 2·95 (N–H), 5·85, 5·92 (alicyclic ketone; acetophenone-type ketone), and 6·02 μ (lactam). The mechanism of this surprising cyclisation is not clear: it will be investigated further. However, the structure of the diketolactam (XVII) was proved by Huang-Minlon reduction to the *cis*-lactam containing no carbonyl groups, though the yield was lower than that of the corresponding *trans*-lactam from the monoketo-lactam (XVIII) (Gates, personal communication). The poor yield is apparently due, in a way not very well understood, to side reactions caused by the presence of the carbonyl group at $C_{(4)}$. Analogous behaviour may be found in the Huang-Minlon reduction of 2-carboxymethyl- and 2-cyanomethyl-2-phenyl*cyclo*hexanone which yielded only phenyl*cyclo*hexane (Carton and Woods, *J. Amer. Chem. Soc.*, 1952, **74**, 5126).



(XV) (XVI*a*; R = H) (XVI*b*; R = Me) (XVII) (XVIII) (XIX)

It was apparent that the vigorous conditions used to reduce both carbonyl groups of the diketo-lactam (XVII) caused considerable destruction by opening of the lactam ring, possibly accompanied by complete removal of the substituents in the "open" product. On reduction of the crude *cis*-lactam with lithium aluminum hydride an oily secondary amine was obtained and methylation with formaldehyde–formic acid gave *N*-methylmorphinan (XIX) identical in melting point and that of its hydrochloride with the compound described by Grewe and Mondon (*loc. cit.*). The sulphate did not depress the melting point of an authentic sample kindly supplied by Prof. R. Grewe. The micro-

infra-red spectra of the two sulphates were very kindly measured by Dr. Elkan Blout of the Polaroid Corporation and found to be identical.

Although the mechanism of the cyclisation to form the *cis*-diketo-lactam (XVII) is not clear, it is evident that inversion of configuration at $C_{(12)}$ in the acetoxy-amide (VII*c*) must have taken place. It is not possible to conceive of epimerisation at $C_{(11)}$ owing to the absence of any activating influence upon this point. We therefore deduce an important point regarding the stereochemistry of the hydrochloride of (VII*a*) obtained by catalytic reduction of the 10-oximino-derivative (V) in the presence of hydrochloric acid. Since for steric reasons the $C_{(10)}$ and $C_{(12)}$ bonds in the lactam must be *cis* (cf. Protiva and Sorm, *Coll. Czech. Chem. Comm.*, 1948, **13**, 428; *Chem. Abs.*, 1949, **43**, 1730; Cronyn, *J. Org. Chem.*, 1949, **14**, 1013; Ginsburg, *ibid.*, 1950, **15**, 1003), and since inversion at $C_{(12)}$ must occur during the cyclisation to give the steric arrangement at $C_{(10)}$, $C_{(11)}$, and $C_{(12)}$ shown in (XVII), the substituted 10-amino-group and the 11-hydrogen atom, *before cyclisation*, must be *cis* to each other. For a *trans*-junction in the octalin system under discussion, this requires that the 10-amino- or substituted 10-amino-group shall assume the equatorial conformation. It may therefore be seen that, whatever primary product of the reduction of the 10-oximino-compound (V) is formed, the stable configuration to be expected is the one in which the 10-amino-group is equatorial. Whilst this argument is plausible, one cannot completely exclude the possibility, in view of the known racemisation of acylamino-acids by hot acids, that the configuration at $C_{(10)}$ changes *during* the cyclisation. A very small amount of an isomeric amine hydrochloride was isolated from the reduction of (V), presumably differing from (VII*a*) in configuration at $C_{(10)}$.

Experiments are being continued with methoxylated analogues of some of the compounds described above with a view of accomplishing the total synthesis of morphine.

Experimental

Improved Michael Condensation Procedures : trans-3-*Keto*-2-*phenyl*cyclo*hexylacetic Acid.*—A mixture of 2-phenyl*cyclo*hex-2-enone (50 g.), benzyl malonate (150 g.), and potassium *tert.*-butoxide (prepared from 1·33 g. of potassium and 20 ml. of *tert.*-butyl alcohol) was kept at 60° for 3 hr., then overnight at room temperature. Acetic acid (2·5 ml.) was added and then ethyl acetate to a volume of 250 ml. Palladium–charcoal (10%; 13 g.) was added and the mixture was hydrogenated at room temperature at an initial pressure of 60 lb./sq. in. (1 hr.). After filtration and evaporation the residue was heated at 170—180° for 10 min. in order to effect decarboxylation of the malonic acid. The residue was dissolved in ether and extracted several times with 10% sodium carbonate solution. Acidification gave a precipitate of *trans*-3-keto-2-phenyl*cyclo*hexylacetic acid (55 g., 82% overall), m. p. 125° (from benzene). The *dibenzyl* ester of the malonic acid was crystallised from the mixture which in some runs solidified; it had m. p. 91—92° (from ethanol) (Found : C, 76·0; H, 6·3. $C_{29}H_{28}O_5$ requires C, 76·3; H, 6·2%).

trans-3-Keto-2-(2 : 3-dimethoxyphenyl)*cyclo*hexylacetic acid was obtained similarly in 88% overall yield.

trans-3-*Keto*-2-*phenyl*cyclo*hexylacetonitrile.*—2-Phenyl*cyclo*hex-2-enone (90 g.), benzyl cyanoacetate (150 g.), and potassium *tert.*-butoxide (2·32 g. of potassium; 35 ml. of *tert.*-butyl alcohol) were treated as above. trans-α-*Cyano*-3-*keto*-2-*phenyl*cyclo*hexylacetic acid*, m. p. 110—112° (from 30% acetic acid), was obtained (Found : C, 70·2; H, 5·7. $C_{15}H_{15}O_3N$ requires C, 70·0; H, 5·8%). Decarboxylation at 190—200° for 10 min. in the presence of powdered soft glass gave trans-3-*keto*-3-*phenyl*cyclo*hexylacetonitrile* (97 g., 86%), which on recrystallisation from butanol melted at 102—103° (Found : C, 78·9; H, 6·9. $C_{14}H_{15}ON$ requires C, 78·9; H, 7·0%).

α-Cyano-α-2-(2 : 3-dimethoxyphenyl)-3-keto*cyclo*hexylacetic acid, identical with the product described in Part III (*loc. cit.*), was similarly obtained, in 94% yield. The acid was decarboxylated as above. Upon evaporative distillation (bath-temp. 250°; 0·01 mm.), *trans*-2-(2 : 3-dimethoxyphenyl)-3-keto*cyclo*hexylacetonitrile was obtained as an oil (82% overall yield). The *semicarbazone* melted at 181—182° (from ethanol) (Found : N, 20·8. $C_{15}H_{18}ON_4$ requires N, 20·7%).

(*a*, 1) *Introduction of an Amino-group at* $C_{(10)}$.—trans-α-*Amino*-3-*keto*-2-*phenyl*cyclo*hexylacetic acid* (II*a*). Methyl 3-keto-2-phenyl*cyclo*hexyl-α-nitroacetate (57·5 g.) was hydrogenated in ethanol (680 ml.) at 100°/120 atm. (initial) in the presence of Raney nickel (20 g.), 94% of the theoretical amount of hydrogen being absorbed during 1 hr. The catalyst was filtered off and the filtrate concentrated (water-pump) to 300 ml. Aqueous sodium hydroxide (20%; 100 g.)

was added and the mixture kept at room temperature for 24 hr. The pH was adjusted to 5·5 with acetic acid and the precipitate was filtered. The *amino-acid* had m. p. 185—188° (from water or aqueous ethanol) (yield 50%) [Found: C, 68·2; H, 6·8; amino-N (van Slyke), 5·7. $C_{14}H_{17}O_3N$ requires C, 68·0; H, 6·9; amino-N, 5·6%].

trans-α-*Amino*-2-(2 : 3-*dimethoxyphenyl*)-3-*keto*cyclo*hexylacetic acid* (II*b*), prepared analogously, had m. p. 200—210° (decomp.) (from water) (Found: N, 4·5. $C_{16}H_{21}O_5N$ requires N, 4·6%)

trans-3-*Keto*-2-*phenyl*cyclo*hexyl*-α-*phthalimidoacetic acid* (III). The amino-acid (15 g.) and phthalic anhydride (9 g.) were heated in benzene (35 ml.) for 1 hr. The benzene was allowed to evaporate and the temperature was raised to 180—190° for 30 min. After cooling, the *phthalimido-acid* was crystallised from ethanol; it had m. p. 227° (decomp.) (yield 60%) (Found: C, 69·8; H, 5·1. $C_{22}H_{19}O_5N$ requires C, 70·0; H, 5·1%).

trans-2-(2 : 3-*Dimethoxyphenyl*)-3-*keto*cyclo*hexyl*-α-*phthalimidoacetic acid*, prepared analogously (yield 75%), had m. p. 219—220° (decomp.) (from ethanol) (Found: C, 66·1; H, 5·7. $C_{24}H_{23}O_7N$ requires C, 65·9; H, 5·3%).

Cyclisation of (III). The phthalimido-acid (III) (1 g.) was treated with concentrated sulphuric acid (5 ml.), kept on the steam-bath for 10 min., then poured on ice. The product was extracted with ether, the extract was washed with sodium hydrogen carbonate solution to remove any uncyclised acid, and the solvent was evaporated. The residue of trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketo*-10-*phthalimidophenanthrene* (IV) after recrystallisation from acetic acid melted at 188° (Found: C, 73·5; H, 4·4. $C_{22}H_{17}O_4N$ requires C, 73·5; H, 4·7%).

4-*Ethylene glycol ketal of* trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketo*-10-*oximinophenanthrene* (V). To the 4-ethylene glycol ketal of *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketophenanthrene (27·4 g.) (Part III) was added a solution of sodium ethoxide (2·76 g. of sodium; 55 ml. of dry ethanol). The mixture was chilled in ice, and *n*-amyl nitrite (18·4 ml.) was added in one portion. The mixture became cherry-red and was set aside at 0° for 48 hr. with occasional shaking. Acetic acid (8 ml.) and water (100 ml.) were added and the mixture was extracted with ether. The ethereal solution was extracted several times with Claisen alkali, the extracts were acidified with acetic acid, and the oily product was taken up in ether. The *product* crystallised from the ethereal solution (17 g.). An additional crop (2·5—4 g.) was obtained after concentration of the solution. Upon recrystallisation from a large volume of ethanol, an analytical sample could be obtained, with m. p. 182—184° (decomp.; green melt) (Found: C, 66·8; H, 5·7. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 5·7%). The crude crystalline material was very slightly soluble in most solvents. After being washed with ether, it was sufficiently pure to be used for further transformations.

4-*Ethylene glycol ketal of* trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketo*-5 : 6-*dimethoxy*-10-*oximinophenanthrene* was obtained similarly from the 4-ethylene glycol ketal of the corresponding methoxy-diketone, in 62% yield, and with m. p. 192—195° (decomp.) (from ethanol) (Found: C, 62·2; H, 5·5. $C_{18}H_{21}O_6N$ requires C, 62·2; H, 6·0%).

trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-4 : 9-*diketo*-10-*phthalimidophenanthrene* (IV). (i) Compound (V) (6 g.), suspended in alcohol (200 ml.), was hydrogenated (10 hr.) in the presence of 10% palladium–charcoal (1 g.) at 60 lb./sq. in. (initial). The solvent was distilled off in a high vacuum (bath-temp. ≯20°). The 4-ethylene glycol ketal (VI*a*) (5·4 g.) of 10-amino-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketophenanthrene was obtained as a brown oil.

When hydrochloric acid (2·2 ml.) was added to the above mixture before hydrogenation, the *hydrochloride of* trans-10-*amino*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketophenanthrene* (VII) (5·5 g.) was obtained with m. p. 228—231° (from ethanol–ether) (Found: C, 63·3; H, 6·2; Cl, 13·5. $C_{14}H_{16}O_2NCl$ requires C, 63·3; H, 6·0; Cl, 13·4%). An isomeric hydrochloride, m. p. 190—192° (from methanol), was isolated from the mother-liquor (0·1 g.) (Found: C, 63·0; H, 6·0; Cl, 13·2. $C_{14}H_{16}O_2NCl$ requires C, 63·3; H, 6·0; Cl, 13·4%).

(ii) The ketal (VI*a*) (1·9 g.) and phthalic anhydride (1·16 g.) were heated together at 170—190° for 30 min. After cooling, the glass was dissolved in acetic acid and the solution deposited crystals (2·1 g.), m. p. 217—219°, of the 4-*ethylene glycol ketal* of *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketo-10-phthalimidophenanthrene (Found: C, 71·6; H, 5·2. $C_{24}H_{21}O_5N$ requires C, 71·5; H, 5·2%).

(iii) The phthalimido-ketal (500 mg.) was kept in ethanol (25 ml.) containing hydrochloric acid (1 ml.) at 50—60° for 5 hr. The solvent was removed. The residue, recrystallised from acetic acid, had m. p. 187—188°. This product did not depress the m. p. of *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketo-10-phthalimidophenanthrene (IV) (see above).

(*a*, 2) *Introduction of an Ester Group at* $C_{(10)}$.—*4-Ethylene glycol ketal of* trans-*10-ethoxalyl-*1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro-*4 : 9-*diketophenanthrene* (VI*b*). To a stirred mixture, kept at 40—45°, of the 4-ethylene glycol ketal (26 g.) of *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketophenanthrene, ethyl oxalate (30 g.), sodium hydride (5 g.), and dry ether (125 ml.), in an atmosphere of nitrogen, a few drops of dry ethanol were added to initiate reaction. The mixture was cooled in ice, water was added, and the solvent layer was separated and extracted with several portions of 3% sodium hydroxide solution. The combined alkaline extracts were acidified with cold dilute hydrochloric acid. The *product* (2·8 g.) had m. p. 99—102° (from ethanol) (Found: C, 67·3; H, 5·9. $C_{20}H_{22}O_6$ requires C, 67·0; H, 6·2%). When sodium methoxide was used as condensing agent the yield was 10—15%.

4-Ethylene glycol ketal of ethyl trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro-*4 : 9-*diketophenanthrene-*10-*carboxylate* (VI*c*). The 10-ethoxalyl compound (10 g.) was decarbonylated by powdered soft glass at 160—170° (10 min.). The *product* (7·2 g.) had m. p. 117—118° (from aqueous methanol) (Found: C, 68·6; H, 6·4. $C_{19}H_{22}O_5$ requires C, 69·1; H, 6·7%).

Reduction of (VI*c*). Compound (VI*c*) (10 g.) in dry ethanol (100 ml.) was hydrogenated in the presence of 10% palladium–charcoal (1 g.), at 70°/60 lb./sq. in. (initial), 1 mol. of hydrogen being absorbed during 3 hr. The *4-ethylene glycol ketal* (7·1 g.) of ethyl *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-9-hydroxy-4-ketophenanthrene-10-carboxylate (7·1 g.) melted at 102—103° (from heptane) (Found: C, 68·8; H, 7·1. $C_{19}H_{24}O_5$ requires C, 68·7; H, 7·3%).

Acid cleavage of (VI*c*). A mixture of (VI*c*) (1 g.), 95% ethanol (25 ml.), water (7 ml.), and concentrated hydrochloric acid (0·2 ml.) was kept at 60° for 1 hr., then overnight at room temperature. After neutralisation with solid sodium hydrogen carbonate, filtration, and dilution with water, crystals were isolated (m. p. 90°). Admixture with 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketophenanthrene gave a large depression in m. p. but admixture with its 4-ethylene glycol ketal gave no depression.

The 4-ethylene glycol ketal of *trans*-10-ethoxalyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketo-5 : 6-dimethoxyphenanthrene was obtained analogously, except that the reaction was carried out in ether–benzene, as an oil in 85% yield and was used in the next reaction without further purification.

4-Ethylene glycol ketal of ethyl trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro-*4 : 9-*diketo-*5 : 6-*dimethoxyphenanthrene-*10-*carboxylate*. Decarbonylation of the ethoxalyl compound as above gave the 10-*carbethoxy*-derivative (75%), m. p. 131—132° (from ethanol) (Found: C, 64·1; H, 6·6. $C_{21}H_{26}O_7$ requires C, 64·6; H, 6·7%).

Alkaline cleavage of the 4-ethylene glycol ketal of ethyl trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro-*4 : 9-*diketo-*5 : 6-*dimethoxyphenanthrene-*10-*carboxylate*. The ester (0·3 g.) was refluxed with 50% aqueous potassium hydroxide (3 ml.) for 2 hr. (cf. Bachmann, Cole, and Wilds, *J. Amer. Chem. Soc.*, 1940, **62**, 833). Water was added. The product which crystallised had m. p. 137—138°. On admixture with authentic 4-ethylene glycol ketal of *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketo-5 : 6-dimethoxyphenanthrene (m. p. 137—139°), it melted at 137—139°.

Lactone (VIII). A mixture of methyl oxalate (2·4 g.), sodium methoxide (1·4 g.) and benzene (10 ml.), was refluxed under nitrogen for 10 min. To this was added a solution of *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4-ketophenanthrene (2 g.) in benzene (15 ml.). An orange colour developed immediately. The mixture was stirred under nitrogen at room temperature for 5 hr. A yellow suspension was obtained. This was filtered and the solid sodium salt washed with benzene and ether. The salt was insoluble in water. It was suspended in dioxan (50 ml.), and hydrochloric acid added to just neutral reaction, causing the free ester to dissolve. Sodium chloride was filtered off and water added to the filtrate. A crystalline *lactone* (VIII) (1·8 g.) was obtained, having m. p. 250° (decomp. with previous sintering) (from acetic acid) (cf. Bachmann, Fujimoto, and Wick, *loc. cit.*), insoluble in ethanol and giving no reaction with ferric chloride in ethanol but in dioxan an immediate deep red colour (Found: C, 75·4; H, 5·5. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·6%).

Lactone O-methyl ether (IX). The lactone (VIII) (1 g.) was treated with ethereal diazomethane. The lactone dissolved and the *O*-methyl ether, m. p. 146—147° (from ethanol), separated.

Lactone (X). This substance was obtained similarly from methyl oxalate (2·4 g.), sodium methoxide (1·4 g.), and *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketophenanthrene (2·1 g.) in benzene. In this case a cherry-red gel was obtained. The brick-red sodium salt was dissolved in water and acidified with dilute hydrochloric acid. The *lactone* (X) (1·1 g.), crystallised from methanol, had m. p. 256—257° (decomp.). The ethanolic solution gave a

negative ferric chloride test but its solution in dioxan gave a very deep red-brown colour with this reagent (Found: C, 71·9; H, 4·5. $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%).

cis-12-2′-*Cyanoethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4-*keto*-3-*methoxalylphenanthrene*. This compound was obtained similarly from methyl oxalate (1·2 g.), sodium methoxide (0·6 g.), and *cis*-12-2′-cyanoethyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4-ketophenanthrene (see below) (1·27 g.) in benzene. After 4 hr.' stirring under nitrogen at room temperature, an orange gel was obtained. Water was added and the benzene solution was extracted with 2% sodium hydroxide solution. Upon acidification of the alkaline extract and scratching, the oil solidified. The *product* had m. p. 131—133° (from methanol) and gave an immediate cherry-red colour with ferric chloride. The yield was 0·7 g. (quantitative, based on unrecovered material) (Found: N, 4·1. $C_{20}H_{21}O_4N$ requires N, 4·1%).

Methyl cis-12-2′-*cyanoethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4-*ketophenanthrene*-3-*carboxylate* was obtained in the usual way. It had m. p. 130° (from ethanol) and gave a purple colour with ferric chloride, which developed slowly (Found: N, 4·5. $C_{19}H_{21}O_3N$ requires N, 4·5%).

(*a*, 3) *Alkylation of* 2-*Phenyl*cyclo*hexanone*.—*Model experiments*. (i) *With chloroacetonitrile*. To a refluxing suspension of sodamide (2·5 g.) in dry ether (35 ml.) was added during 1 hr. a solution of 2-phenyl*cyclo*hexanone (10 g.) in dry ether (17·5 ml.) and dry benzene (7·5 ml.). After an additional hr. of refluxing (until ammonia evolution was complete), the milky solution was cooled and a solution of chloroacetonitrile (6·1 g.) in dry ether (17·5 ml.) was added. The mixture became warm and refluxing was maintained for 3 hr. After cooling, water was added, and the organic layer was separated and washed with water and dried. After evaporation of the solvents, the residue was distilled *in vacuo*. The product (8·5 g.) was a yellow oil, b. p. 145—150°/0·4 mm., which consisted mainly of 2-*cyanomethyl*-2-*phenyl*cyclo*hexanone* (Found: C, 78·8; H, 7·2. $C_{14}H_{15}ON$ requires C, 78·8; H, 7·1%), as shown by the practically quantitative preparation of a benzylidene derivative.

2-*Keto*-1-*phenyl*cyclo*hexylacetic acid*. The above nitrile (1·4 g.) was refluxed with acetic acid (28 ml.) and concentrated hydrochloric acid (14 ml.) for 12 hr. (cf. Bachmann and Wick, *J. Amer. Chem. Soc.*, 1950, **72**, 3388). The acid isolated formed colourless needles, m. p. 133—134° (from acetic acid) (Found: C, 72·4; H, 7·0. Calc. for $C_{14}H_{16}O_3$: C, 72·4; H, 6·9%). Boekelheide (*ibid.*, 1950, **72**, 712) reports m. p. 130·5—131°.

(ii) *With ethyl iodoacetate*. Ethyl iodoacetate (18 g.) was used as the alkylating agent under similar conditions. The oily product (11 g.) boiled at 160—170°/2 mm. and formed an orange 2 : 4-*dinitrophenylhydrazone*, m. p. 163—164° (from ethanol) (Found: C, 59·8; H, 5·5. $C_{22}H_{24}O_6N_4$ requires C, 60·0; H, 5·5%). The position of the carbethoxymethyl group in this substance was not ascertained; attempted preparation of the benzylidene derivative showed that the product was a mixture of isomers apparently containing the carbethoxymethyl group in either of the two positions adjacent to the carbonyl group. Boekelheide (*loc. cit.*) reported alkylation with ethyl bromoacetate without, however, indicating the degree of possible alkylation in both positions.

(iii) *With* 2-*benzyloxyethyl methanesulphonate* (cf. Newman and Magerlein, *J. Amer. Chem. Soc.*, 1947, **69**, 943). To a stirred solution of methanesulphonyl chloride (114 g.) and ethylene glycol monobenzyl ether (137 g.) in dry ether (200 ml.) at −10° was added pyridine (112 g.) during 4 hr. The temperature was then allowed to rise and the mixture was stirred at 0° for 2 hr. Cold water was added and the product was extracted with ether, the ethereal solution was washed and dried, and the solvent was removed *in vacuo*. Small samples of the *sulphonate* could be distilled without decomposition (b. p. 120—125°/0·01 mm.) (Found: S, 13·9. $C_{10}H_{14}O_4S$ requires S, 13·8%). The material as obtained from this preparation was sufficiently pure for further work.

Alkylation was carried out as described above, with [for the same amount of 2-phenyl*cyclo*hexanone (10 g.)] 2-benzyloxyethylmethanesulphonate (16 g.) in ether (25 ml.) and benzene (25 ml.). Distillation yielded an oil consisting of practically only one isomer, 2-2′-*benzyloxyethyl*-2-*phenyl*cyclo*hexanone* (16 g.), b. p. 170—175°/0·01 mm. (Found: C, 81·5; H, 7·5. $C_{21}H_{24}O_2$ requires C, 81·8; H, 7·8%). The *semicarbazone* melted at 212—213° (from ethanol) (Found: N, 11·6. $C_{22}H_{27}O_2N_3$ requires N, 11·5%). The veratrylidene and benzylidene derivatives were prepared in nearly quantitative yield but neither crystallised.

2-2′-*Hydroxyethyl*-2-*phenyl*cyclo*hexanone*. The above benzyl ether (6·2 g.) in alcohol (50 ml.) was hydrogenated in the presence of 10% palladium charcoal (0·6 g.) at 60 lb./sq. in. (initial). One mol. of hydrogen was taken up during 2 hr. Distillation gave a colourless oily *alcohol*, b. p. 115—120°/0·05 mm. (Found: C, 77·2; H, 8·1. $C_{14}H_{18}O_2$ requires C, 77·0; 8·3%).

Alkylation of trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4-*ketophenanthrene*. To a refluxing suspension of sodamide (1·2 g.) in dry ether (25 ml.) and benzene (15 ml.) was added, during 1 hr., a solution of the ketone (5 g.) in ether (15 ml.) and benzene (5 ml.). The mixture was refluxed for 5 hr. (ammonia evolution). After cooling, methyl iodide (6 g.) was added. Almost immediately sodium iodide was precipitated. Refluxing was continued for 3 hr. and the product was isolated in the usual way. The product, b. p. 128—134°/0·05 mm., consisted mainly of 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4-*keto*-12-*methylphenanthrene* (Found : C, 83·9; H, 8·7. $C_{15}H_{18}O$ requires C, 84·1; H, 8·4%). The *semicarbazone* had m. p. 250—251° (from butanol) (Found : N, 15·8. $C_{16}H_{21}ON_3$ requires N, 15·5%). The 3-*benzylidene* compound, obtained in 77% yield from the oil, had m. p. 200—201° (from ethanol) (Found : C, 87·0; H, 7·6. $C_{22}H_{22}O$ requires C, 87·4; H, 7·3%).

Chloroacetonitrile and ethyl iodoacetate were also used as alkylating agents in this case but chromatography (on alumina) of the 2 : 4-dinitrophenylhydrazone mixture obtained from the reaction products showed the presence of three products in each case. These reactions were therefore not studied further.

cis-12-2′-*Cyanoethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4-*ketophenanthrene* (XII*a*).—To a solution of *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4-ketophenanthrene (2·8 g.) in dioxan (25 ml.) were added 30% benzyltrimethylammonium hydroxide (Triton B) (0·3 ml.) and a solution of acrylonitrile (1 g.) in dioxan (3 ml.), and the mixture was stirred for 2 hr. At the start, the temperature rose to 40°. Dilute hydrochloric acid was added, the mixture was extracted with ether, and the solvents were evaporated. The solid residue was taken up in boiling heptane and the solution was filtered to remove a small amount of bis-2-cyanoethyl adduct (0·2 g.). From the filtrate was obtained the crystalline *product*, m. p. 110—112° (from heptane or ethanol) (75%) (Found : N, 5·4. $C_{17}H_{19}ON$ requires N, 5·5%). 3 : 12-*Bis*-2′-*cyanoethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydrophenanthrene* had m. p. 165—166° (from ethanol) (Found : N, 9·2. $C_{20}H_{22}ON_2$ requires N, 9·5%). Only unchanged starting material was recovered from the mother-liquor.

The adduct (XII*a*) (0·3 g.), veratraldehyde (0·25 g.), ethanol (3·4 ml.), and 15% aqueous sodium hydroxide (0·8 ml.) were kept at room temperature for 1 week. The yellow 3-*veratrylidene* derivative, recrystallised from ethanol, then from *n*-propanol, had m. p. 163—165° (yield 75%) (Found : C, 77·8; H, 6·9. $C_{26}H_{27}O_3N$ requires C, 77·8; H, 6·7%).

cis-12-2′-*Carboxyethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4-*ketophenanthrene* (XII*b*).—The compound (XII*a*) (1·14 g.), acetic acid (7·5 ml.), concentrated hydrochloric acid (2·5 ml.), and water (25 ml.) were refluxed under nitrogen for 15 hr. Water was added and the *acid* was recrystallised from heptane–benzene (yield, 90%). Recrystallised finally from aqueous methanol it had m. p. 110—112° (Found : C, 75·4; H, 7·5. $C_{17}H_{20}O_3$ requires C, 75·0; H, 7·3%). The *semicarbazone* melted at 219° (decomp.) (from ethanol) (Found : N, 12·8. $C_{18}H_{23}O_3N_3$ requires N, 12·8%).

cis-12-2′-*Cyanoethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketophenanthrene* (XI*a*).—Compound (I*b*) (21·4 g.) was dissolved in dioxan (100 ml.), and Triton B (30%; 1 ml.) was added. Acrylonitrile (8 ml.) in dioxan (20 ml.) was added with stirring; the temperature rose to 42°. After 2 hr. the mixture was acidified with dilute hydrochloric acid and the solvent was removed *in vacuo*. The residue was dissolved in ethanol (150 ml.). The *product* crystallised slowly [m. p. 112—113° (from ethanol); yield, 11·5 g.]. A second crop of product (2·3 g.) could be isolated from the mother-liquor (Found : C, 76·5; H, 6·4. $C_{17}H_{17}O_2N$ requires C, 76·3; H, 6·4%). The 3 : 10-*dibenzylidene* derivative, prepared in 90% yield, had m. p. 206—207° (from acetic acid) (Found : C, 84·2; H, 5·8; N, 3·1. $C_{31}H_{25}O_2N$ requires C, 84·0; H, 5·6; N, 3·2%). The 3 : 10-*dipiperonylidene* derivative melted at 230—231° (from acetic acid) (Found : N, 2·9. $C_{33}H_{25}O_6N$ requires N, 2·6%) and the 3 : 10-*diveratrylidene* derivative at 182—183° (from propanol) (Found : C, 74·5; H, 5·5; N, 2·9. $C_{35}H_{33}O_6N$ requires C, 74·6; H, 5·8; N, 2·5%).

cis-12-2′-*Carboxyethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketophenanthrene* (XI*b*).—From the nitrile (XI*a*) (5·1 g.) was obtained, as described for the hydrolysis of (XII*a*), the *acid* (4·5 g.), m. p. 155° (from aqueous methanol) (Found : C, 71·6; H, 6·3. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%).

Reduction of (XI*b*).—Compound (XI*b*) (3 g.) was hydrogenated in acetic acid (50 ml.) in the presence of 10% palladium charcoal (0·3 g.) at 60—70°/60 lb./sq. in. (initial). Two mols. of hydrogen were absorbed during 2 hr. The product, isolated in the usual way, had m. p. 110—112° (from aqueous methanol) and proved to be identical with (XII*b*) (see above).

Huang-Minlon Reduction of (XII*b*).—The keto-acid (XII*b*) (5 g.) was refluxed with di-

ethylene glycol (50 ml.), potassium hydroxide (4 g.), and 85% hydrazine hydrate (6 ml.) for 90 min. The condenser was then removed, the temperature was raised to 195—200°, and the mixture refluxed for 5 hr. The cooled mixture was acidified with dilute hydrochloric acid. The resulting precipitate of cis-12-2′-*carboxyethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydrophenanthrene* (XIII*a*), recrystallised from aqueous methanol, had m. p. 111—113° (90%) (Found : C, 79·3; H, 8·5. $C_{17}H_{22}O_2$ requires C, 79·0; H, 8·6%).

cis-12-2′-*Aminoethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydrophenanthrene* (XIII*b*).—The acid (XIII*a*) (2 g.) was refluxed with thionyl chloride (10 ml.) in benzene (10 ml.) for 1 hr. Volatile material was removed *in vacuo* at <30°; benzene (5 ml.) was added and the mixture was again subjected to vacuum-distillation. The yellow residue was dissolved in acetone (10 ml.) and to the ice-cold solution was added sodium azide (2·5 g.) in water (6 ml.) in one portion, with ice-cooling. After 10 min. the mixture was diluted with water, and the oil which precipitated was taken up in ether. The ethereal extract was washed with aqueous sodium hydrogen carbonate solution and dried (Na_2SO_4). The ether was evaporated off at the water pump at <25°. The brown azide was warmed with acetic acid (15 ml.) (<80°) until nitrogen evolution ceased (about 30 min.), then heated at 100° for 1 hr. Concentrated hydrochloric acid (10 ml.) was added and the mixture refluxed for 12 hr. The mixture was concentrated *in vacuo*. The hydrochloride, m. p. 250° (75%), of the amine crystallised and was washed with ether but not purified further. The *picrate*, prepared from an aqueous solution of the hydrochloride, had m. p. 182—183° (decomp.) (from aqueous ethanol) (Found : C, 57·6; H, 5·4; N, 12·4. $C_{22}H_{26}O_7N_4$ requires C, 57·6; H, 5·7; N, 12·2%).

cis-12-2′-*Dimethylaminoethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydrophenanthrene* (XIII*c*).—The crude hydrochloride of (XIII*b*) (1·4 g.) in water (3 ml.) was basified with sodium hydroxide and extracted with ether. The ether was evaporated and to the residue were added with cooling 90% formic acid (1·3 g.) and 30% formaldehyde solution (0·56 ml.). The mixture was placed in a bath at 90—100°. Evolution of carbon dioxide began within a few sec.; the flask was removed from the bath until the evolution subsided (10 min.), and then heated at 95—100° for 8 hr. Concentrated hydrochloric acid (2 ml.) was added and the mixture was concentrated at the water-pump for 2 hr. at 100°. The crystalline material which formed (1·5 g.) was converted into the *picrate* of the tertiary amine in ethanolic solution (Found : C, 59·0; H, 6·2; N, 11·4. Calc. for $C_{24}H_{30}O_7N_4$: C, 59·3; H, 6·2; N, 11·5%). This had m. p. 187—188·5° (from ethanol), alone or mixed with an authentic sample of (XIII*c*), kindly furnished by Prof. R. Grewe. Mixed with an authentic specimen of the *trans*-isomer of (XIII*c*), kindly supplied by Dr. Marshall Gates, it melted at 169—175°.

1 : 2 : 9 : 10 : 11 : 12-*Hexahydropyrrolidino*(2′ : 3′-4 : 12)*phenanthrene* (XV).—When the acid (XII*b*) was treated with thionyl chloride as described for (XIII*a*) a product melting at about 140° with the properties of a lactone was obtained. On attempted crystallisation from ethanol, no crystalline material could be recovered, apparently owing to ester formation.

To the keto-acid (XII*b*) (1 g.) in benzene (5 ml.) was added thionyl chloride (5 ml.) and the mixture kept for 48 hr. at −5° to −10°. The solvent and excess of chloride were removed in a high vacuum and the Curtius reaction carried out as described above for (XIII*a*). After 12 hr.' refluxing with concentrated hydrochloric acid, the mixture was concentrated *in vacuo* and to the residual brown oil was added water (2 ml.). The mixture was extracted with ether to remove non-basic material. The aqueous solution was strongly basified with sodium hydroxide and extracted with ether. The ethereal solution was extracted with 2N-hydrochloric acid. Upon concentration of the acid layer, the hydrochloride of (XV) was obtained as a hygroscopic brown oil in 40% overall yield.

1 : 2 : 9 : 10 : 11 : 12-*Hexahydro*-9-*ketopyrrolidino*(2′ : 3′-4 : 12)*phenanthrene* (XVI*a*).—*Method* (*a*). The acid chloride was prepared from (XI*b*) as described above for (XII*b*) at −5° to −10°. The azide was prepared and converted into the amine as above but in this case it was possible to isolate the *pyrrolidine* in 20% overall yield as crystals, m. p. 87—89° (from hexane) (Found : C, 80·4; H, 7·1; N, 5·9. $C_{16}H_{17}ON$ requires C, 80·3; H, 7·2; N, 5·9%).

N-*Methyl derivative* (XVI*b*). Methylation was carried out by Bachmann and Fornefeld's method (*J. Amer. Chem. Soc.*, 1951, **73**, 52). The pyrrolidine (XVI*a*) (1·5 g.) was treated in ethyl methyl ketone (3 ml.) with methyl sulphate (0·8 g.) at room temperature. After 10 min. the solution became slightly warm and after several hr. two layers were formed The mixture was left overnight, the lower layer then crystallising. After a total of 16 hr., the mixture was refluxed for 1 hr., water (5 ml.) was added, and refluxing was continued for 3 additional hr. Water was added, followed by aqueous sodium hydroxide. A solid amine was precipitated; it was taken up in ether. Removal of the ether yielded the yellow N-*methylpyrrolidine* (XVI*b*),

m. p. 132—133° (from ethanol) (overall yield, 20%) (Found : N, 5·5. $C_{17}H_{19}ON$ requires N, 5·5%). This autoxidised rapidly in solution, to give brown material.

Method (*b*). The acid (XI*b*) (6·45 g.) was treated with an excess of diazomethane in ether. Immediately after the nitrogen evolution ceased, acetic acid was added. The ethereal solution was washed with sodium hydrogen carbonate solution, then water, and dried (Na_2SO_4). Evaporation yielded an oil which was treated in ethanol (25 ml.) with 100% hydrazine (10·5 ml.). After 3 hr.' refluxing, the volatile material was removed *in vacuo* and the glassy residue was dissolved in 3N-hydrochloric acid (180 ml.). Ether (100 ml.) was added to form an upper layer, the mixture chilled in an ice-bath, and sodium nitrite (10 g.) in water (90 ml.) was added with cooling. The ethereal layer was separated and the aqueous layer extracted once with ether. The combined ethereal solutions were washed with water, and sodium hydrogen carbonate solution, and dried (Na_2SO_4). The ether was removed *in vacuo* (below 25°) and the residual brown oil was treated as in method (*a*) with acetic acid. The subsequent working up was as in method (*a*) and the pyrrolidine (XVI*a*) was obtained in 20% overall yield. The product thus obtained was purer than that formed by method (*a*). Admixture gave no m. p. depression.

Ketal of (XI*a*).—Compound (XI*a*) (2 g.), ethylene glycol (6 ml.), toluene-*p*-sulphonic acid (0·1 g.), and toluene (20 ml.) were refluxed for 7·5 hr., during which 4·5 ml. were collected as a lower layer in an azeotropic separator. The mixture was cooled and poured into dilute potassium carbonate solution. After ether-extraction and removal of the solvents, the 4 : 9-*bisethylene glycol ketal* of 12-2′-cyanoethyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketophenanthrene crystallised on trituration with a fresh portion of ether [yield, 1·7 g.; m. p. 136—137° (from ethanol)]. There was no carbonyl absorption in the infra-red (Found : C, 70·9; H, 7·1. $C_{21}H_{25}O_4N$ requires C, 71·0; H, 7·1%).

When the ketal was heated for 30 min. with 20% aqueous ethanol containing a trace of hydrochloric acid, the starting material (XI*a*) was recovered.

Cyanoethylation of 3-*Keto*-2-*phenyl*cyclo*hexylacetonitrile*.—The nitrile (10·4 g.) and Triton B (1 ml.) in dioxan (80 ml.) were treated with acrylonitrile (4 ml.) in dioxan (20 ml.), the temperature rising to 37°. After 2 hr.' stirring, the mixture was acidified with dilute hydrochloric acid and the dioxan removed *in vacuo*. The residue was dissolved in ethanol (100 ml.) and crystalline material was obtained in the hot solution. After filtration at 40°, 2 : 6 : 6-*tris*-2′-*cyanoethyl*-3-*keto*-2-*phenyl*cyclo*hexylacetonitrile* (3 g.) was obtained, having m. p. 161—162° (from ethanol) (Found : N, 12·6. $C_{21}H_{23}ON_3$ requires N, 12·6%).

cis-12-*Carbamylmethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketophenanthrene* (XI*c*).—*Method a*. To the oily acid chloride prepared from 1 g. of (XI*b*) was added benzene (50 ml.), and dry ammonia was passed through the solution at 5—10° for 2 hr. The amide, precipitated as tan-coloured crystals (70%), had m. p. 205° (from aqueous acetic acid).

Method b. To the acid (XI*b*) (1 g.) was added an excess of diazomethane in ether. After 5 min., the solution was evaporated and the residue was dissolved in dry ethanol (10 ml.). Dry ammonia was passed through the solution at 0° for 3 hr. The mixture was kept at room temperature for 48 hr., giving the *amide*, m. p. 205—206° (from dilute acetic acid) (90%) (Found : C, 71·5; H, 6·6. $C_{17}H_{19}O_3N$ requires C, 71·6; H, 6·7%).

Halogeno-amides from (VI*a*).—Compound (VI*a*) (1 g.) was added to a solution of sodium acetate (2·5 g.) in acetic acid (5 ml.). To this ice-cold solution was added slowly with efficient stirring chloroacetyl chloride (3 ml.). The 4-*ethylene glycol ketal* of *trans*-10-chloroacetamido-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketophenanthrene was deposited as crystals, m. p. 199—200° (from ethanol) (Found : Cl, 9·8. $C_{18}H_{20}O_4NCl$ requires Cl, 10·1%).

The *bromoacetoamido-ketal*, obtained analogously from bromoacetyl chloride, had m. p. 210—211° (from ethanol) (Found : Br, 20·5. $C_{18}H_{20}O_4NBr$ requires Br, 20·3%).

The *iodoacetamido-ketal* had m. p. 200—201° (from ethanol) (Found : I, 30·0. $C_{18}H_{20}O_4NI$ requires I, 28·8%).

Hydrolysis of the ketals in aqueous ethanol containing a catalytic amount of hydrochloric acid afforded the corresponding free halogenoamides (VII*b*) : *chloro-amide*, m. p. 186° (from methanol) (Found : Cl, 11·5. $C_{16}H_{16}O_3NCl$ requires Cl, 11·6%); *bromo-amide*, m. p. 200—201° (from ethanol) (Found : Br, 22·7. $C_{16}H_{16}O_3NBr$ requires Br, 22·9%); *iodo-amide*, m. p. 178—179° (from ethanol) (Found : I, 31·7. $C_{16}H_{16}O_3NI$ requires I, 32·0%).

Attempted intramolecular cyclisation of each of the three free halogeno-amides in the presence of alkaline catalysts, such as sodamide, potassium *tert.*-butoxide, lithium amide, under a variety of conditions, failed. Bromination of the bromo-amide, m. p. 200—201°, in acetic acid solution with one mol. of bromine followed by treatment with activated zinc led to no definable product.

trans-10-*Acetoxyacetamido*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketophenanthrene* (VII*c*).—The amine hydrochloride (cf. VII*a*) (3 g.) was suspended in cold chloroform (50 ml.) and pyridine (2 g.) was added and the mixture was stirred with cooling until all of the solid had dissolved. Acetylglycolloyl chloride (1·8 g.) in chloroform (10 ml.) was added with stirring and cooling during 1 hr., and the mixture finally refluxed for 30 min. The solution was cooled and washed several times with water. The solvent was evaporated. The *amide* (3·4 g.), crystallised from ethanol or toluene, had m. p. 205° (Found : C, 65·5; H, 5·8. $C_{18}H_{19}O_5N$ requires C, 65·6; H, 5·8%). We are indebted to Dr. Orrie M. Friedman for suggesting the use of acetylglycolloyl chloride.

Diketo-lactam (XVII).—(*a*) The acetoxy-amide (VII*c*) (4 g.), ethylene glycol (10 g.), toluene (25 ml.), benzene (14 ml.), and toluene-*p*-sulphonic acid (0·1 g.) were heated together under reflux for 9 hr., during which 6·5 ml. of liquid were collected as lower layer in an azeotropic separator. The mixture was cooled and solid sodium methoxide was added to neutralise the acid present. After being washed with water, the organic layer was evaporated to dryness; the residue was triturated with light petroleum. The solid *ketal* obtained (2·3 g.) recrystallised from toluene and had m. p. 240—241° (Found : C, 69·1; H, 6·0. $C_{18}H_{19}O_4N$ requires C, 69·0; H, 6·1%). The infra-red absorption spectrum showed bands at 2·95, 5·93, and 6·02 μ.

(*b*) The ketal (2 g.) on treatment with aqueous ethanol containing hydrochloric acid at 60° for 2 hr. gave the free *diketo-lactam* (XVII), m. p. 257—258° (from ethanol or benzene–light petroleum) (Found: C 71·2; H, 5·5. $C_{16}H_{15}O_3N$ requires C, 71·4; H, 5·6%). The infra-red absorption spectrum showed bands at 2·95, 5·85, 5·92, and 6·02 μ. A mixture with its ketal melted at 213—248°.

N-*Methylmorphinan* (XIX).—(*a*) The diketo-lactam (XVII) (250 mg.) was refluxed with diethylene glycol (6 ml.), potassium hydroxide (0·42 g.), and 100% hydrazine (1 g.) for 8 hr. The condenser was removed and the internal temperature was raised to 195—200° and kept thereat for 2 hr., and finally the mixture was refluxed for 4 hr. The resulting dark brown solution was cooled and poured into an excess of dilute hydrochloric acid. The resulting lactam was obtained as a gum (140 mg.); it was triturated alternately with dilute acid, dilute alkali, and water and then dried *in vacuo*. The infra-red absorption spectrum showed a band at 6·01 μ (corresponding to the lactam) but the bands at 5·85 and 5·92 μ were absent.

(*b*) The gummy lactam was dissolved in dry ether (25 ml.) and refluxed with lithium aluminium hydride (1 g.) in dry ether (25 ml.) for 145 hr. The excess of reducing agent was decomposed by an equivalent amount of water, and the ethereal solution was washed with alkali and with water and dried (KOH). Evaporation *in vacuo* afforded a yellow oil (68 mg.).

(*c*) Formic acid (90%; 0·5 ml.) was carefully added to the above amine (68 mg.) with ice-cooling, and then 30% formaldehyde solution (0·2 ml.). The mixture was heated at 95—100° for 8 hr. After cooling, hydrochloric acid was added and the mixture concentrated *in vacuo*. The semi-solid residue was treated with acetone and ether. *N*-Methylmorphinan hydrochloride (47 mg.), m. p. 229—231°, was obtained (Found : Cl, 12·7. Calc. for $C_{17}H_{23}NCl$: Cl, 12·8%). Grewe and Mondon (*loc. cit.*) report m. p. 231—233°.

The hydrochloride was converted into the free base, m. p. 59—60°. Grewe and Mondon report m. p. 61°. The sulphate, m. p. 205° (from alcohol–ether), on admixture with an authentic sample (m. p. 205°), kindly supplied by Prof. R. Grewe, gave no m. p. depression. The micro-infra-red absorption spectrum, carried out with single crystals of the specimens of *N*-methylmorphinan sulphate, conclusively demonstrated the identity of the specimens over the whole absorption range.

A portion of this work was presented at the Milwaukee meeting of the American Chemical Society, April, 1952. We acknowledge with thanks the co-operation of Dr. Marshall Gates and Prof. Rudolf Grewe in supplying various authentic specimens and of Dr. Elkan Blout in the measurement of the infra-red absorption spectrum of *N*-methylmorphinan sulphate. We thank also Mr. Alfred Löffler for superlative preparative assistance which contributed in large measure to the progress of this work. Some of this work is included in a thesis submitted by Raphael Pappo to the Hebrew University, Jerusalem, in partial fulfilment of the requirements of the Ph.D. degree.

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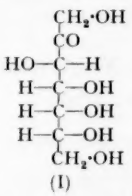
REHOVOT, ISRAEL. [*Received, January 26th,* 1953.]

312. *The Synthesis of Sugars from Simpler Substances. Part VI.* Enzymic Synthesis of* D-*Idoheptulose.*

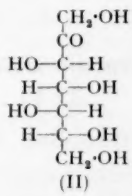
By P. A. J. Gorin and J. K. N. Jones.

An enzymic preparation from peas catalyses the reaction of D-threose with triose phosphate to give D-idoheptulose, identified as D-idoheptulosan.

In Part V,* it was shown that D-erythrose combines with triose phosphate in the presence of an enzyme preparation from the pea (Stumpf, *J. Biol. Chem.*, **1948**, **176**, 233) to give sedoheptulose (I). It was of interest to determine whether or not this is a general type of reaction, and particularly whether D-threose would undergo a similar condensation. Accordingly, D-threose was condensed with triose phosphate under the conditions specified by Hough and Jones (*J.*, **1953**, **342**) An examination at intervals, of portions of the reaction solution on paper chromatograms, indicated that material possessing the colour reactions of a heptulose (cf. Klevstrand and Nordal, *Acta Chem. Scand.*, **1950**, **4**, 1320) was produced. After 90 hr. suitable manipulations, including heating with dilute acid, gave a mixture of sugar (20%) and anhydride (80%) (Pratt, Richtmyer, and Hudson, *J. Amer. Chem. Soc.*, **1952**, **74**, 2210). The latter is stable when heated with alkalis, but the reducing sugars, such as idoheptulose (II), glucose, and fructose, which are present in the solution, are destroyed. The solution was therefore heated with barium hydroxide, filtered, freed from barium and other ions, and concentrated to a syrup. D-Idoheptulosan was isolated by chromatography on paper and identified by its analysis, its rate of movement on paper chromatograms, its colour reaction with the orcinol spray, its m. p. and mixed m. p., and its *X*-ray diffraction pattern (for determination of which we thank Mr. D. A. Brown) (cf. Pratt, Richtmyer, and Hudson, *loc. cit.*).



(I)



(II)

The synthesis of D-idoheptulose is a further example of the production of a sugar with the D-xylulose configuration on $C_{(1)}$, $C_{(2)}$, $C_{(3)}$, and $C_{(4)}$, by the action of aldolase on a mixture of hexose diphosphate and an aldehyde. Aldolase is thus an enzyme which will transfer a triose fragment (very probably dihydroxyacetone phosphate) from D-fructose 1 : 6-diphosphate to an aliphatic aldehyde with the resultant formation of an optically active ketose, which possesses the D-xylulose configuration on the first four carbon atoms.

Experimental

The following solvents were used in chromatographic separations on Whatman No. 1 paper : (*a*) ethyl acetate–acetic acid–water (9 : 2 : 2); (*b*) *n*-butanol–ethanol–water (40 : 11 : 19), both by vol. *p*-Anisidine hydrochloride was used as a general spray to detect sugars; orcinol–trichloroacetic acid solution (Klevstrand and Nordal, *loc. cit.*) was used to detect heptulose and heptulosan. Evaporation of solutions was carried out under reduced pressure.

Synthesis of D-*Idoheptulose.*—D-Threose (8 g.) was prepared from D-xylose (30 g.) *via* calcium D-xylonate (Hudson and Isbell, *J. Amer. Chem. Soc.*, **1929**, **51**, 2225) by the procedure used for the preparation of D-erythrose from D-arabinose (cf. Overend, Stacey, and Wiggins, *J.*, **1949**, 1358). Ionic material was removed from the crude tetrose preparation by passage of the solution through columns of Amberlite resins IR120 and IR4B. A sample of the product, when separated on a paper chromatogram [solvent (*b*)] showed one main spot (R_F 0·40), which gave a yellowish-brown colour and moved faster than did D-erythrose (R_F 0·33), and a faint pink spot corresponding to xylose.

* Part V, *J.*, 1953, 342.

D-Threose (6 g.) and the sodium salt of hexose diphosphate (8 g.) were dissolved in water (300 c.c.) and the pH adjusted to 7·5 by 0·1N-sodium hydroxide. Crude aldolase solution (Hough and Jones, *J.*, 1952, 4053) (75 c.c.) from peas (250 g.) was added and the mixture kept at 20° for 90 hr. The solution was heated at 90° for 30 min., filtered, and concentrated to a syrup which was dissolved in water and filtered from a small amount of protein. Examination of a small portion of the solution on the paper chromatogram [solvent (*a*)] showed the presence of a heptulose, detected by spraying with orcinol and heating. It moved at the same rate as galactose. The filtrate was passed down a column of Amberlite IR120 resin, the acid effluent (50 c.c.) added to sulphuric acid (2N; 50 c.c.), and the mixture heated at 90° for 3½ hr. in order to convert the heptulose into the equilibrium mixture of heptulose (20%) and heptulosan (80%). The solution was then made alkaline by the addition of barium hydroxide and heated at 90° for 2 hr. The cooled solution was filtered, before and after acidification with cold dilute sulphuric acid, and then deionised by passage down a column of Amberlite resin IR4B. The effluent was concentrated to a syrup (170 mg.), which was examined chromatographically [solvent (*a*)]; it then contained a material which gave a positive test for heptulose (Nordal and Klevstrand, *loc. cit.*) and moved to the same position on the chromatogram as did an authentic specimen of idoheptulosan. Its rate of movement was 0·86 relative to ribose. As the syrup did not crystallise, it was fractionated on a sheet of paper [solvent (*a*)], and the appropriate section of the paper was eluted with methanol. The syrup (81 mg.) thus obtained was similarly refractionated [solvent (*b*)] and the purified product (32 mg.) recrystallised from ethanol or dioxan; it then had m. p. and mixed m. p. 172°, $[\alpha]_D^{20}$ −34° ±8° (*c*, 0·3) (Found: C, 43·9; H, 6·1. Calc. for $C_7H_{12}O_6$: C, 43·8; H, 6·3%).

The authors thank Dr. N. K. Richtmyer for the gift of a specimen of D-idoheptulosan, the Chemical Society for a grant, and the City of Bristol Education Authorities for a Scholarship (to P. A. J. G.).

THE UNIVERSITY, BRISTOL. [*Received, February 4th*, 1953.]

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313. *Anodic Syntheses. Part VIII.* New Syntheses of 3 : 13 : 19-Trimethyltricosanoic Acid.*

By R. P. LINSTEAD, B. R. SHEPHARD, B. C. L. WEEDON, and (in part) J. C. LUNT.

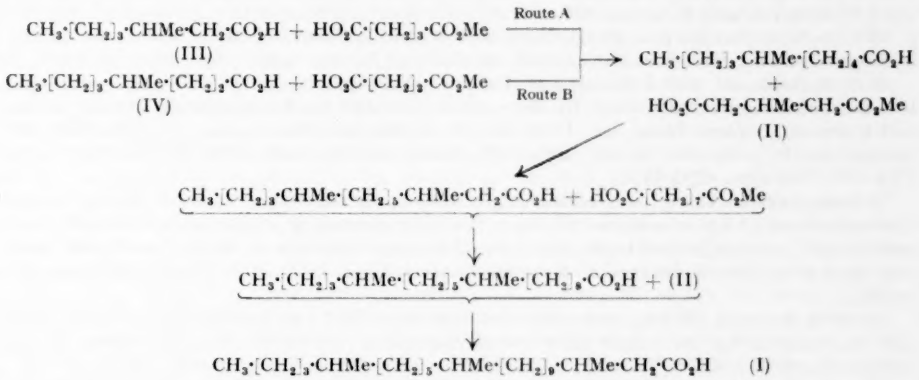
The anodic method for the synthesis of branched-chain fatty acids has been used for preparation of (±)-3 : 13 : 19-trimethyltricosanoic acid. The routes employed are capable of extension to the preparation of pure optical isomers.

WHEN injected intraperitoneally in guinea-pigs, a number of synthetic branched-chain fatty acids cause granulomatous lesions (Ungar, Coulthard, and Dickenson, *Brit. J. Exp. Path.*, 1948, **29**, 322; Brownlee, *Ann. Reports*, 1948, **45**, 292) similar to those produced by Anderson's "phthioic acid" from the lipins of dried tubercle bacilli (Spielman and Anderson, *J. Biol. Chem.*, 1935—36, **112**, 759). "Phthioic acid," formerly believed to be an enantiomorph of 3 : 13 : 19-trimethyltricosanoic acid (I) (Polgar and Robinson, *J.*, 1945, 389), is now known to be a complex mixture, but the structure of the natural acid responsible for the cytological activity has not yet been fully determined (Polgar and Robinson, *Chem. and Ind.*, 1951, 685; Cason and Sumrell, *J. Biol. Chem.*, 1951, **192**, 405; Cason, Freeman, and Sumrell, *ibid.*, p. 415).

With one exception (2 : 13 : 17 : 21-tetramethyldocosanoic acid; Polgar, Robinson, and Seijo, *J.*, 1949, 1545) all synthetic acids tested biologically have been (±)-mixtures, in contrast to the natural acids which are optically active. It is therefore of interest to determine whether, with tubercle-forming acids such as 3 : 13-dimethyl- and 3 : 13 : 19-trimethyl-tricosanoic acid, activity is associated with all, or only one, of the various enantiomorphs. The syntheses so far described of these two acids (Polgar and Robinson, *loc. cit.*; David, Polgar, and Robinson, *J.*, 1949, 1541; Moroe, *J. Pharm. Soc. Japan*, 1950,

* Part VII, *J.*, 1952, 3624.

70, 416; 1951, **71**, 123) are unsuitable for the preparation of all the various stereoisomers required to elucidate the relationship between biological and optical activity. However,



anodic routes, such as those illustrated in the above reaction scheme, would be capable of giving all the isomers with known configurations. Each stage involves crossed coupling of a fatty acid with a half-ester, and since none of these intermediates is α-substituted, coupling would occur with complete retention of asymmetric centres in the starting materials (for references see Weedon, *Quart. Reviews*, 1952, **6**, 380). Both (+)- and (−)-form of methyl hydrogen β-methylglutarate (II) are readily available (Part IV, *J.*, 1951, 1130) and their stereochemical relation to D-glyceraldehyde has been established (Ställberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, 1948, **25**, *A*, No. 10). The (−)-isomers of 3-methylheptanoic (III) (Levene and Marker, *J. Biol. Chem.*, 1932, **95**, 1; Ställberg-Stenhagen, *Arkiv Kemi*, 1950, **2**, 95) and 4-methyloctanoic acid (IV) (Levene and Marker, *loc. cit.*, p. 153) have been described, and no doubt their diastereoisomers could be obtained by standard methods.

The present paper describes syntheses of (±)-3 : 13 : 19-trimethyltricosanoic acid which were undertaken to confirm the feasibility of the routes proposed above. The molar proportions of half-ester to monocarboxylic acid used in each of the electrolyses, and the yields of the resulting branched-chain acid formed by cross-coupling, are given in the Table. The expected products formed by symmetrical coupling of the components were also isolated.

Syntheses of branched-chain acids.

Acid product	Molar proportion of half-ester to acid	Yield (%)
6-Methyldecanoic (route A)	3 : 1	36
,, (route B)	4 : 1	32
3 : 9-Dimethyltridecanoic	4 : 1	50
10 : 16-Dimethyleicosanoic	4 : 1	55
3 : 13 : 19-Trimethyltricosanoic	5 : 1	20

Experimental

Percentage yields, except those of diacids or diesters, are based on the total amount of monocarboxylic acid introduced.

Electrolyses.—The mixture of half-ester and monocarboxylic acid was electrolysed in technical absolute methanol to which sufficient sodium had been added to neutralise 2% of the total acids used. Two cells, A and B, were employed. These consisted of cylindrical glass vessels containing two platinum plates, placed 1—2 mm. apart, as electrodes. In cell A the electrodes measured 4 × 2·5 cm., and in cell B 8 × 5 cm. A current (*ca.* 0·1—0·2 amp./sq. cm. anode current density) was passed until the electrolyte became slightly alkaline. The cell contents were neutralised by the addition of glacial acetic acid, and the solvent was evaporated. The residue was then either distilled or hydrolysed, and the products were separated into neutral and acidic fractions.

Half-esters.—Methyl hydrogen glutarate, b. p. 107°/0·3 mm., n_D^{23} 1·4372, was prepared in 83% yield by heating equimolar quantities of glutaric anhydride (Caunt, Crow, Haworth, and Vodoz, *J.*, 1950, 1631) and methanol on a steam-bath for *ca.* 2 hr. Methyl hydrogen succinate was prepared similarly from succinic anhydride (Shriner and Struck, *Org. Synth.*, Coll. Vol. II, p. 560), methyl hydrogen β-methylglutarate as described in Part II (*J.*, 1950, 3331), and methyl hydrogen azelate as described by Schmidt and Shirley (*J. Amer. Chem. Soc.*, 1949, **71**, 3804).

3-*Methylheptanoic Acid.*—Hexan-2-ol (Barrow and Atkinson, *J.*, 1939, 638) was converted into 2-bromohexane in 73% yield, by the method described for 2-bromodecane (Prout, Cason, and Ingersoll, *J. Amer. Chem. Soc.*, 1948, **70**, 298; Hsueh and Marvel, *ibid.*, 1928, **50**, 855); the bromide had b. p. 78—80°/90 mm., n_D^{22} 1·4421 (Ellis and Reid, *ibid.*, 1932, **54**, 1674, give b. p. 77·8—78·1°/90 mm., n_D^{25} 1·4432).

2-Bromohexane (139 g.) was added dropwise to a stirred, boiling solution of ethyl sodiomalonate (from 19·4 g. of sodium and 139 g. of ethyl malonate) in anhydrous alcohol (420 c.c.), and the mixture was heated under reflux for 15 hours. Isolation of the product in the usual way gave ethyl 2-methylhexane-1 : 1-dicarboxylate (157 g., 77%), b. p. 86—87°/0·5 mm., n_D^{17} 1·4307.

Heating the ester (50·0 g.) and potassium hydroxide (30 g.) in alcohol (150 c.c.) and water (30 c.c.) under reflux for 1 hour gave 2-methylhexane-1 : 1-dicarboxylic acid (32·6 g., 85%), needles, m. p. 91·5—93·5° (Found : equiv., 94·8. Calc. for $C_9H_{16}O_4$: equiv., 94·1).

The dicarboxylic acid (50·0 g.) was heated at 165—185° until evolution of carbon dioxide ceased (*ca.* 40 min.). Distillation of the residue gave 3-methylheptanoic acid (36·4 g., 95%), b. p. 121°/15 mm., n_D^{16} 1·4276 (Found : equiv., 144·4. Calc. for $C_8H_{16}O_2$: equiv., 144·2).

4-*Methyloctanoic Acid.*—4-Hydroxy-4-methyloctanoic lactone, prepared (57% yield) from ethyl lævulate, was converted into ethyl 4-methyloct-3- and -4-enoate (63% yield) (cf. Wilson, *J. Amer. Chem. Soc.*, 1945, **67**, 2161). After sulphur-containing impurities had been removed (Raney nickel), the unsaturated esters were hydrogenated over Adams' catalyst at atmospheric temperature and pressure (cf. Cason, Adams, Bennett, and Register, *ibid.*, 1944, **66**, 1764). Hydrolysis of the product gave 4-methyloctanoic acid in 75% yield, b. p. 140°/17 mm. [Levene and Marker, *J. Biol. Chem.*, 1932, **95**, 153, give b. p. 149°/22 mm. for the (−)-isomer]. The *tribromoanilide* crystallised from alcohol in needles, m. p. 116° (Found : Br, 50·8. $C_{15}H_{20}ONBr_3$ requires Br, 51·0%).

6-*Methyldecanoic Acid.*—(*a*) A solution of 3-methylheptanoic acid (36 g.) and methyl hydrogen glutarate (110 g.) in methanol (270 c.c.) was electrolysed (cell B). Isolation and hydrolysis of the crude product gave 6-methyldecanoic acid (16·3 g.), b. p. 127°/1·5 mm., n_D^{23} 1·4381 (Wilson, *loc. cit.*, gives b. p. 160—164°/17 mm., n_D^{21} 1·4393) [*p*-bromophenacyl ester, plates (from methanol), m. p. 50° (*idem, loc. cit.*, gives m. p. 51°)], and 5 : 8-*dimethyldodecane* (7·8 g., 31%), b. p. 130°/40 mm., n_D^{25} 1·4270 (Found : C, 84·1; H, 15·1. $C_{14}H_{30}$ requires C, 84·8; H, 15·2%).

(*b*) A solution of 4-methyloctanoic acid (53 g., 0·33 mole) and methyl hydrogen succinate (176 g., 1·33 mole) in methanol (400 c.c.) was electrolysed (cell B). Isolation and hydrolysis of the crude product gave : (i) 5 : 10-*Dimethyltetradecane* (10·0 g., 27%), b. p. 140°/15 mm., n_D^{20} 1·4342 (Found : C, 84·9; H, 15·2. $C_{16}H_{34}$ requires C, 84·9; H, 15·1%). (ii) An acidic fraction which was extracted thoroughly with light petroleum (b. p. 40—60°). Separation of the insoluble portion and crystallisation from water gave adipic acid (23·5 g., 24%), m. p. 153°. The petroleum extract was dried and evaporated; distillation of the residue gave 6-methyldecanoic acid (20 g.), b. p. 135°/0·6 mm., n_D^{24} 1·4370 (Found : equiv., 184. Calc. for $C_{11}H_{22}O_2$: equiv., 186). The *p*-bromophenacyl ester had m. p. 50·5°, undepressed on admixture with a specimen from (*a*).

3 : 9-*Dimethyltridecanoic Acid.*—Electrolysis of 6-methyldecanoic acid (30·0 g., 0·16 mole) and methyl hydrogen β-methylglutarate (105·3 g., 0·67 mole) in methanol (180 c.c.) in 2 batches (cell A), and isolation and hydrolysis of the products as described in the preceding experiment gave 5 : 14-*dimethyloctadecane* (4·7 g., 18%), b. p. 115°/0·2 mm., n_D^{24} 1·4436 (Found : C, 84·7; H, 15·0. $C_{20}H_{42}$ requires C, 85·0; H, 15·0%), crude ββ′-dimethylsuberic acid, m. p. 70—80° (35 g., 60%), and 3 : 9-*dimethyltridecanoic acid* (20·0 g.), b. p. 154°/0·2 mm., n_D^{20} 1·4480. Titration (equiv., 220, 221) showed that the last acid was contaminated with some of the dicarboxylic acid. A sample was purified for analysis by precipitation of the dicarboxylic acid as the lead salt from alcohol. The recovered dimethyltridecanoic acid had n_D^{23} 1·4471 (Found : C, 73·8; H, 12·3%; equiv., 240, 241. $C_{15}H_{30}O_2$ requires C, 74·3; H, 12·5%; equiv., 242). The *tribromoanilide* after many crystallisations from methanol had m. p. 115°, not raised by further recrystallisation (Found : N, 2·6. $C_{21}H_{32}ONBr_3$ requires N, 2·5%).

10 : 16-*Dimethyleicosanoic Acid.*—Electrolysis (cell A) of 3 : 9-dimethyltridecanoic acid

(17·0 g., 0·07 mole) and methyl hydrogen azelate (56·5 g., 0·28 mole) in methanol (100 c.c.), and isolation and hydrolysis of the products, gave 5 : 11 : 14 : 20-*tetramethyltetracosane* (3·0 g., 21%), b. p. 150°/5 × 10^{-4} mm., n_D^{24} 1·4508 (Found: C, 85·2; H, 14·8. $C_{28}H_{58}$ requires C, 85·0; H, 15·0%), thapsic acid (20·0 g., 37%), m. p. 122°, and 10 : 16-*dimethyleicosanoic acid* (13·0 g.), b. p. 150°/10^{-4} mm., n_D^{20} 1·4568 (Found: C, 77·7; H, 12·8. $C_{22}H_{44}O_2$ requires C, 77·6; H, 13·0%). The equiv. (Found: 328. Calc.: 340) showed that the last acid was slightly contaminated with thapsic acid. No attempt was made to purify it further before the next stage as dicarboxylic acids do not give products of the Kolbe type at the anode (cf. Weedon, *loc. cit.*).

3 : 13 : 19-*Trimethyltricosanoic Acid.*—Electrolysis (cell A) of 10 : 16-dimethyleicosanoic acid (10·2 g., 0·03 mole) and methyl hydrogen β-methylglutarate (24·0 g., 0·15 mole) in methanol (50 c.c.), isolation, and distillation of the product gave methyl ββ′-dimethylsuberate (11·9 g., 68%), b. p. 100°/0·3 mm., n_D^{17} 1·4388 (Linstead, Lunt, and Weedon, *J.*, 1950, **3333**, give $n_D^{18\cdot5}$ 1·4376), and a fraction (6·0 g.), b. p. 180—200°/10^{-3} mm., n_D^{23} 1·4520—1·4588. The latter was heated under reflux for 12 hours with alcoholic potassium hydroxide (20% w/v). Separation of the neutral and the acidic products in the usual way gave 5 : 11 : 28 : 34-*tetramethyloctatriacontane* (2·2 g., 25%), b. p. 200°/10^{-3} mm., n_D^{25} 1·4570 (Found: C, 85·35; H, 14·8. $C_{42}H_{86}$ requires C, 85·3; H, 14·7%), and 3 : 13 : 19-trimethyltricosanoic acid (2·2 g.), b. p. 190°/10^{-3} mm., n_D^{18} 1·4594 (Found: C, 78·3; H, 13·1%; equiv., 392. Calc. for $C_{26}H_{52}O_2$: C, 78·7; H, 13·2%; equiv., 396) (Polgar and Robinson, *J.*, 1945, 389, give n_D^{17} 1·4620; Moroe, *loc. cit.*, gives n_D^{18} 1·4600).

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314. *Organic Peroxides. Part I. The Preparation of Alkyl Hydroperoxides from Hydrogen Peroxide.*

By A. G. Davies, R. V. Foster, and A. M. White.

The preparation of alkyl hydroperoxides by the reaction of concentrated hydrogen peroxide with (*a*) alcohols, (*b*) carboxylic esters, (*c*) 2-butyl sodium sulphate, and (*d*) olefins has been investigated. It is suggested that reactions of (*a*), (*b*), and (*c*), and the corresponding reactions of alkyl halides, involve nucleophilic substitution by hydrogen peroxide usually by a unimolecular mechanism, *viz.* :

$$R\overset{\curvearrowright}{-}X \overset{\text{slow}}{\rightleftharpoons} R^+ + X^- \qquad R^+ + HO{\cdot}OH \xrightarrow{\text{fast}} RO{\cdot}OH + H^+$$

In the reaction of olefins the alkyl cation is formed by protonation, the subsequent step being as above.

Two types of reaction for the preparation of alkyl hydroperoxides are known. The first, the autoxidation of a hydrocarbon, occurs most readily at the α-position to a benzene ring (*e.g.*, as in 1 : 2 : 3 : 4-tetrahydronaphthalene) or a double bond (*e.g.*, as in *cyclo*hexene), and its mechanism has been interpreted as that of a homolytic chain reaction (Farmer, Bloomfield, Sundralingham, and Sutton, *Trans. Faraday. Soc.*, 1942, **38**, 348).

The second method involves the reaction of hydrogen peroxide with (*a*) tertiary alcohols in the presence of a trace of concentrated sulphuric acid (Criegee and Dietrich, *Annalen*, 1948, **560**, 135), (*b*) alkyl sulphates ($RR'SO_4$) in the presence (*e.g.*, R = R′ = Me; Baeyer and Villiger, *Ber.*, 1901, **34**, 738) or absence (*e.g.*, R = Bu^t, R′ = H; Milas and Surgenor, *J. Amer. Chem. Soc.*, 1946, **68**, 205) of alkali, or (*c*) triarylmethyl halides (*e.g.*, triphenylmethyl chloride; Wieland and Maier, *Ber.*, 1931, **64**, 1205). The preparation of alkyl hydroperoxides by the action of hydrogen peroxide on certain secondary and tertiary alcohols and on the carboxylic esters and olefins derived from them is now reported.

In Criegee and Dietrich's preparation, the tertiary alcohol is treated with 90% hydrogen peroxide containing a trace of concentrated sulphuric acid at room temperature for some hours. It is stated (Criegee and Dietrich, *loc. cit.*; Criegee, *Fortschr. chem. Forsch.*, 1950, **1**, 508—566, especially p. 530) that primary and secondary alcohols are unreactive under these conditions. We have now shown, however, that, although simple saturated aliphatic secondary alcohols (*e.g.*, butan-2-ol, and 3:3-dimethylbutan-2-ol) can be recovered unchanged after such treatment, (secondary) α-substituted benzyl alcohols, as well as tertiary alcohols are converted into the corresponding alkyl hydroperoxides. *tert.*-Butyl, *tert.*-amyl, 1-*iso*butyl-1-methylpropyl, 1-phenylethyl, diphenylmethyl, and 1:2:3:4-tetrahydro-1-naphthyl hydroperoxides have been prepared in good yield by this method. In all cases reaction takes place in the presence of sulphuric acid, but some alcohols react in the presence of the weaker acid, formic acid, or even in the absence of catalyst. The alkyl groups above are arranged in the approximate order of increasing reactivity. The optically active 1:2:3:4-tetrahydro-1-naphthol gives the optically inactive hydroperoxide. All the hydroperoxides named above, except 1-*iso*butyl-1-methylpropyl, have been previously described.

In the study of the reactivity of hydrogen peroxide towards carboxylic esters, we have used chiefly the readily available alkyl hydrogen phthalates because their sodium salts form a homogeneous solution in concentrated hydrogen peroxide. When 1:2:3:4-tetrahydro-1-naphthyl or diphenylmethyl hydrogen phthalate is dissolved in 90% hydrogen peroxide containing sodium hydrogen carbonate, the corresponding hydroperoxide soon separates in good yield. From the optically active 1:2:3:4-tetrahydro-1-naphthyl ester the inactive hydroperoxide is formed. Only a small amount of 1-*iso*butyl-1-methylpropyl hydroperoxide could be isolated, and no reaction occurred with 1-phenylethyl hydrogen phthalate. Reaction mixtures from methyl or 1-methylheptyl hydrogen phthalate are unstable, but about 70% of the starting material can be recovered after 4 hr. A poor yield of 1:2:3:4-tetrahydro-1-naphthyl hydroperoxide was obtained by stirring the acetate with hydrogen peroxide containing formic acid; the reaction is not therefore restricted to hydrogen phthalates.

The yields of methyl, ethyl, and *iso*propyl hydroperoxides obtained by treatment of the corresponding dialkyl sulphates with strongly alkaline hydrogen peroxide are reported to be low (Eggersglüss, *Angew. Chem.*, 1951, **61**, 72); but treatment of *tert.*-butyl and *tert.*-amyl hydrogen sulphates with 30% hydrogen peroxide gives good yields of a mixture of the corresponding alkyl hydroperoxide and dialkyl peroxide (Milas and Surgenor, *J. Amer. Chem. Soc.*, 1946, **68**, 205, 643). We were unable to obtain 1-methylpropyl hydroperoxide by treating 1-methylpropyl sodium sulphate with neutral 90% or alkaline 30% hydrogen peroxide.

To support the postulation (see Discussion) of the existence of intermediate carbonium ions in the preparations of alkyl hydroperoxides from alcohols and esters, attempts were made to obtain the same products by the addition of hydrogen peroxide to olefins. 2-Methylbut-2-ene with concentrated hydrogen peroxide containing a trace of concentrated sulphuric acid gave *tert.*-amyl hydroperoxide; the hydrogen atom therefore adds to the least alkyl-substituted end of the double bond: $CH_3 \cdot CH{:}CMe \cdot CH_3 + HO \cdot OH \longrightarrow CH_2 \cdot CH_2 \cdot CMe_2 \cdot O \cdot OH$. Similarly the olefin derived from 3:5-dimethylhexan-3-ol (probably 3:5-dimethylhex-2-ene) reacts to form 1-*iso*butyl-1-methylpropyl hydroperoxide, but *cyclo*hexene is unchanged by such treatment.

Criegee and Dietrich (*loc. cit.*) have used the *p*-nitrobenzoates to characterise alkyl hydroperoxides. We prefer, however, to use the previously undescribed 1-alkyl hydrogen 1-monoperphthalates (o-$RO_2 \cdot CO \cdot C_6H_4 \cdot CO_2H$) because estimation of the free-acid group gives confirmation of the equivalent weight of the hydroperoxide. These crystalline derivatives are readily prepared by the use of phthalic anhydride in the presence of pyridine (under which conditions *tert.*-alcohols do not react). Decomposition occurs when the peresters are heated above their melting points, phthalic acid and acetone being among the products of decomposition of the *tert.*-butyl perester. It has also been shown that these compounds catalyse the polymerisation of styrene. These problems are being further investigated. 1-*tert.*-Butyl hydrogen 1-monopersuccinate is also described. Unfortun-

ately the 1-phenylalkyl hydroperoxides do not form stable esters; when this work was carried out, no satisfactory derivatives of such compounds were available.

Discussion

The S_N1 reactions of alkyl halides (Hughes, Ingold, and their co-workers, *J.*, 1933—1952; cf. *Quart. Reviews*, 1951, **5**, 245) and the unimolecular alkyl–oxygen fission reactions of carboxylic esters and of alcohols (Day and Ingold, *Trans. Faraday Soc.*, 1941 **37**, 686; Kenyon and his co-workers, *J.*, 1942—1952) all proceed by the general mechanism :

$$R{-}\overset{\curvearrowright}{X} \underset{}{\overset{\text{slow}}{\rightleftharpoons}} R^+ + X^- \qquad\qquad R^+ + Y^- \xrightarrow{\text{fast}} R{-}Y$$

where X = Cl, etc., R′·CO_2 or HO (R′·CO_2H and $\overset{+}{H}O_2$ under acid conditions), respectively. A study of the relative rates of such reactions permits the arrangement of the various groups R in the following approximate order of increasing reactivity by unimolecular mechanism : Me, Et, Pr^i, Bu^t, CHPhMe, $CHPh_2$.

It is now suggested that all the preparations of alkyl hydroperoxides by the reaction of hydrogen peroxide with alkyl derivatives (R—X; where X = Cl, HO, or $\overset{+}{H_2}O$, R′·CO_2, R′SO_4) involve nucleophilic attack by the HO·OH molecule or HO·O^- ion according to the general equation :

$$HO{-}\overset{\curvearrowright}{\underset{H}{O}} \quad R{-}\overset{\curvearrowright}{X} \longrightarrow HO{\cdot}OR + X^- + H^+$$

and that this takes place usually by a unimolecular mechanism of the type described in the summary.

When the critical complex of such a reaction involves the appearance of charges, this will be favoured by the high polarity of 90% hydrogen peroxide (dielectric constant, 97 at 0°). A rapid bimolecular attack by un-ionised hydrogen peroxide upon the types of molecules which do undergo reaction would appear to be improbable in view of the low basicity of the hydrogen peroxide molecule (Evans and Uri, *Trans. Faraday Soc.*, 1949, **45**, 224).

Triphenylmethyl halides thus react readily with hydrogen peroxide (Wieland and Maier, *loc. cit.*; Pinazzi, *Compt. rend.*, 1948, **226**, 929) probably because electron release by the phenyl groups promotes the reactivity by the S_N1 mechanism. Substitution of a $-T$ group in the *ortho*- or *para*-position in the benzene rings would tend to negate the $+T$ effect of the phenyl groups; thus *p*-nitrotriphenylmethyl chloride is less reactive towards hydrogen peroxide but the reaction is catalysed by stannic chloride which aids the removal of the chloride anion by the formation of the $SnCl_5^-$ ion (Bartlett and Cotman, *J. Amer. Chem. Soc.*, 1950, **72**, 3095).

The reactivity of the various alcohols and carboxylic esters towards hydrogen peroxide follows the sequence given above for the reactivity by the unimolecular mechanism. Again then, such reactions would appear to be unimolecular substitution reactions, *e.g.*

$$Ph{\cdot}CHMe{-}\overset{\curvearrowright}{\underset{}{O}}H_2 \underset{}{\overset{\text{slow}}{\rightleftharpoons}} H_2O + \overset{+}{C}HMe \xrightarrow[H_2O_2]{\text{fast}} PhCHMe{\cdot}O{\cdot}OH + H^+$$

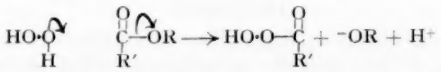
and

$$CHPh_2{-}\overset{\curvearrowright}{O}{\cdot}CO{\cdot}C_6H_4{\cdot}CO_2^- \underset{}{\overset{\text{slow}}{\rightleftharpoons}} C_6H_4(CO_2^-)_2 + \overset{+}{C}HPh_2 \xrightarrow[H_2O_2]{\text{fast}} CHPh_2{\cdot}O{\cdot}OH + H^+$$

(the $B_{AL}1$ mechanism : Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686; Bunton, Hughes, Ingold, and Meigh, *Nature*, 1950, **166**, 680). This conclusion is supported by the observation that optically active 1 : 2 : 3 : 4-tetrahydro-1-naphthol and its hydrogen phthalate yield the inactive hydroperoxide in both cases. In the mechanism postulated the intermediate carbonium ion would be planar, and racemisation would occur at this stage.

The position of the methyl and simple saturated secondary alkyl groups in the sequence of reactivity by a unimolecular mechanism suggests that unimolecular alkyl–oxygen fission

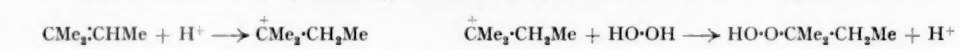
reactions of methyl hydrogen phthalate and 2-octyl hydrogen phthalate would be slow and reaction by an acyl–oxygen fission mechanism more probable. Such a reaction with hydrogen peroxide would lead to the formation of a peracid and an alcohol :



Unfortunately the instability of such reaction mixtures rendered impossible the isolation of any products of reaction.

The reactivity of *tert.*-alkyl sulphates towards the weakly nucleophilic neutral hydrogen peroxide and of methyl and ethyl sulphates towards the more strongly nucleophilic alkaline hydrogen peroxide, may be indicative of the S_N1 and S_N2 mechanisms respectively, both proceeding by alkyl–oxygen fission. The low reactivity of the simple secondary alkyl halides by either of these two mechanisms (Gleave, Hughes, and Ingold, *J.*, **1935**, 226) may afford an explanation of our failure to isolate any *sec.*-butyl hydroperoxide from the reaction between sodium *sec.*-butyl sulphate and hydrogen peroxide

If the postulation of an intermediate carbonium ion is correct, then processes other than dissociation which will produce a carbonium ion in a medium of hydrogen peroxide might also be expected to lead to the formation of alkyl hydroperoxides. An example of this is provided by the preparation of *tert.*-amyl hydroperoxide by the reaction between 2-methylbut-2-ene and hydrogen peroxide in the presence of a trace of sulphuric acid :



The direction of addition of the hydrogen peroxide and the fact that *cyclo*hexene is unreactive under similar conditions, are both in agreement with the known influence of substituents on such a reaction mechanism (Gwyn Williams, *Trans. Faraday Soc.*, **1941**, **37**, 749).

The range of alkyl hydroperoxides which can be prepared by the alkylation of hydrogen peroxide is thus more extensive than has previously been supposed. The reaction of alcohols perhaps affords the most convenient available method of preparation, but appears to be restricted to alcohols with a reactivity approximately equal to or greater than *tert.*-butyl alcohol. The danger of explosion which may accompany such reactions (Criegee and Dietrich *loc. cit.*) is probably caused by the instability of the hydroperoxide towards the acid catalyst, and can be mitigated to some extent by the use of the weakest acid capable of catalysing the reaction. The scope of the methods of preparation described here coincides to some extent with that of the autoxidation of hydrocarbons, because the $+T$ groups which will stabilise an alkyl cation (*e.g.* A), will also stabilise the corresponding

alkyl radical (*e.g.* B). However a $-T$ group, which would not stabilise an alkyl cation to any appreciable extent, will nevertheless stabilise the corresponding free radical (Ingold, *Trans. Faraday Soc.*, **1934**, **30**, 52), and thus the autoxidation reaction may be applicable to a compound RH, whose corresponding derivatives RX might be unreactive by the ionic mechanism suggested here.

Experimental

Light petroleum refers to the fraction with b. p. 40—60°. The preparation and resolution of 1 : 2 : 3 : 4-tetrahydro-1-naphthol and its derivatives have been described previously (Davies and White, *J.*, **1952**, 3300).

Analysis for Peroxidic Oxygen.—The amount of hydroperoxide in mixtures was roughly estimated as follows : A known weight (approx. 0·20 g.) of the impure hydroperoxide was dissolved in glacial acetic acid (10 c.c.), and potassium iodide (1·0 g.) was added. Next morning the liberated iodine was estimated with sodium thiosulphate solution, and comparison made with a blank solution. The accuracy of the method is within approx. ±4%.

Hydrogen Peroxide.—Unstabilised 85—90% hydrogen peroxide was supplied by Messrs. Laporte Chemicals Ltd., Luton. Precautions were taken to minimise the effect of a possible explosion in reactions with this material; detonation never took place, but vigorous decomposition occurred on a few occasions, caused apparently by instability of the organic peroxide produced under the (frequently acid) experimental conditions.

Preparation of Hydrogen Perphthalates and Persuccinates.—The following details illustrate the method of preparation of the 1-alkyl hydrogen 1-monoperphthalates and 1-monopersuccinates. A mixture of *tert.*-butyl hydroperoxide (9 g.), phthalic anhydride (14·8 g.), and pyridine (11·8 g., 1·5 mols.) was set aside for 12 hr. at room temperature, most of the phthalic anhydride dissolving. After 10 min. at 65—68° the clear solution was cooled, diluted with an equal volume of acetone, acidified (Congo-red) with 6N-hydrochloric acid, and then diluted with water. The deposited hydrogen perphthalate was recrystallised from ether–light petroleum giving 1-tert.-*butyl hydrogen* 1-*monoperphthalate* (20·2 g.) as stable, white crystals, m. p. 104—104·5° (decomp.) (Found: C, 61·0; H, 6·0%; equiv., 236. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%; equiv., 238).

Reaction between 85—90% Hydrogen Peroxide and Alcohols.—(i) tert.-*Butyl alcohol.* The alcohol (5 c.c.) was added to hydrogen peroxide (5 c.c.) containing concentrated sulphuric acid (0·05 c.c.), at 0°. After 6 hr. at room temperature, water (15 c.c.) was added, the upper organic layer extracted with light petroleum, and the extract washed and dried (Na_2SO_4). Distillation yielded *tert.*-butyl hydroperoxide (4·8 g.), b. p. 50—54°/45 mm., n_D^{20} 1·3985, n_D^{25} 1·3968. By reaction with phthalic anhydride in the presence of pyridine (see above) this yielded 1-*tert.*-butyl hydrogen 1-monoperphthalate, m. p. 104° (decomp.) (Found: equiv., 238. Calc. for $C_{12}H_{14}O_5$: equiv., 238). A similar reaction with succinic anhydride in the presence of pyridine (experiment by Mr. K. J. Hunter) gave, in good yield, 1-tert.-*butyl hydrogen* 1-*monopersuccinate* as a stable white solid (from ether–light petroleum), m. p. 58—59° (Found: C, 50·0; H, 7·3%; equiv., 195. $C_8H_{14}O_5$ requires C, 50·5; H, 7·4%; equiv., 190).

From a similar reaction mixture, in which 98% formic acid (0·05 c.c.) was used as catalyst, after 72 hr. most of the *tert.*-butyl alcohol (3·5 c.c.) was recovered by salting out with potassium carbonate, but a residue of *tert.*-butyl hydroperoxide (0·30 g.), b. p. 37—38°/19 mm., was obtained, from which was prepared the hydrogen phthalate, m. p. and mixed m. p. 103—104·5° (decomp.). In the absence of any catalyst, the unchanged alcohol was recovered after 21 days and shown by analysis to be free from peroxidic material.

(ii) tert.-*Amyl alcohol.* After 6 hr.' stirring and 16 hr. at room temperature, a mixture of the alcohol (10 c.c.), hydrogen peroxide (10 c.c.), and concentrated sulphuric acid (0·02 c.c.) yielded *tert.*-amyl hydroperoxide (4·36 g.), b. p. 50—51°/20 mm., n_D^{20} 1·4154 (Found: C, 57·9; H, 11·6. Calc. for $C_5H_{12}O_2$: C, 57·7; H, 11·6%). From this hydroperoxide (1 g.), 1-tert.-*amyl hydrogen* 1-*monoperphthalate* (1·5 g.) was obtained as glassy rhombs, m. p. 87—89° (decomp.) (Found: C, 61·4; H, 6·6%; equiv., 252. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·3%; equiv., 252). By reaction of the hydroperoxide (1 g.) with *p*-nitrobenzoyl chloride (1·79 g.) in the presence of pyridine (1·14 g.), tert.-*amyl* p-*nitroperbenzoate* was obtained as pale yellow needles (from aqueous ethanol or light petroleum), m. p. 48·5—49·5° (Found: C, 57·1; H, 6·0; N, 5·8. $C_{12}H_{15}O_5N$ requires C, 56·9; H, 5·9; N, 5·5%).

(iii) 3 : 5-*Dimethylhexan*-3-*ol.* The alcohol, prepared by Clarke's method (*J. Amer. Chem. Soc.*, 1908, **30**, 1144), had b. p. 150—151°/754 mm., 72—74°/50 mm., n_D^{20} 1·4267, n_D^{25} 1·4241. The alcohol (10 c.c.), hydrogen peroxide (10 c.c.), and concentrated sulphuric acid (0·10 c.c.) were stirred for 6 hr., giving 1-iso*butyl*-1-*methylpropyl hydroperoxide* (8·3 g., 88% yield), b. p. 51—52°/2 mm., n_D^{20} 1·4350, n_D^{25} 1·4331, d_4^{25} 0·895 (Found: C, 66·2; H, 12·6. $C_8H_{18}O_2$ requires C, 65·7; H, 12·4%). There was a small unidentified viscous residue (0·85 g.). An attempt to prepare the hydroperoxide via the alkyl hydrogen sulphate (Milas and Surgenor, *loc. cit.*) gave only an olefin, b. p. 113—114°. Doering and Zeiss (*J. Amer. Chem. Soc.*, 1950, **72**, 147) reported an olefin, b. p. 112—115°, as a by-product from the reductive cleavage of 1-*iso*butyl-1-methylpropyl hydrogen phthalate with methylmagnesium bromide.

The hydroperoxide (63 g.), phthalic anhydride (64 g.), and pyridine (51 g.) gave the *hydrogen* 1-*monoperphthalate* (102 g.) as a stable white crystalline solid (from ether–light petroleum), m. p. 87—90° (decomp.), the melting point being dependent upon the rate of heating (Found: C, 65·9; H, 7·8%; equiv., 294. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·5%; equiv., 294).

(iv) 1-*Phenylethanol.* The alcohol (2 g.) was stirred for 6 hr. at 5—10° with hydrogen peroxide (10 c.c.) and concentrated sulphuric acid (0·02 c.c.). Water (20 c.c.) was then added and the product obtained by ether extraction, washing of the extract with dilute sodium hydrogen carbonate solution and distillation. The slightly yellow oil (3·5 g. from 2 preparations),

b. p. 60°/0·05 mm., contained approx. 95% of the hydroperoxide, estimated volumetrically. Aqueous sodium hydroxide (5 c.c.; 75% solution) at 0° was added to the impure hydroperoxide (1·0 g.), acetone (10 c.c.) was added, and the salt was filtered off and washed with acetone. A solution of the salt in water (20 c.c.) was extracted with ether, and then acidified with 3N-acetic acid. Extraction with ether and distillation gave 1-phenylethyl hydroperoxide, b. p. 48°/0·01 mm., n_D^{20} 1·5250 (Found : C, 69·6; H, 7·8. Calc. for $C_8H_{10}O_2$: C, 69·8; H, 7·3%).

From a reaction with 98% formic acid (0·02 c.c.) as catalyst instead of sulphuric acid, a slightly yellow oil (2·0 g.) was recovered, containing 43% of 1-phenylethyl hydroperoxide; a similar experiment with no catalyst gave only 4% of the hydroperoxide. It was not possible to separate the hydroperoxide from unchanged alcohol by distillation.

(v) *Diphenylmethanol.* The alcohol (1·0 g.), as a saturated ethereal solution, was stirred for 6 hr. with hydrogen peroxide (10 c.c.) and concentrated sulphuric acid (0·02 c.c.). The ether extract of the diluted reaction mixture was washed with aqueous sodium hydrogen carbonate solution and dried (Na_2SO_4), yielding diphenylmethyl hydroperoxide (1·1 g.) as needles (from light petroleum) (0·60 g.), m. p. 50—52° (Found : C, 78·0; H, 6·2. Calc. for $C_{13}H_{12}O_2$: C, 78·0; H, 6·0%). Hock and Lang (*Ber.*, 1944, **77**, 257) reported m. p. 51° for the compound obtained by autoxidation of diphenylmethane.

Use of 98% formic acid (0·02 c.c.) instead of sulphuric acid gave material (9 g.) containing 30% of diphenylmethyl hydroperoxide, estimated volumetrically. In the absence of a catalyst a product (1·0 g.) containing 20% of the hydroperoxide was obtained.

(vi) 1 : 2 : 3 : 4-*Tetrahydro*-1-*naphthol.* A mixture of the alcohol (0·50 g.), hydrogen peroxide (10 c.c.), and 98% formic acid (0·02 c.c.) was stirred for 2 hr. and then set aside for 1·5 hr. The solid product was dried and crystallised from light petroleum, giving 1 : 2 : 3 : 4-tetrahydro-1-naphthyl hydroperoxide (0·20 g.), m. p. 54—56° undepressed on admixture with a sample obtained by the autoxidation of tetralin.

In the absence of any catalyst 0·70 g. (from 1 g. of alcohol) of recrystallised hydroperoxide, m. p. 56°, was obtained. This experiment was repeated with the optically active alcohol, $[\alpha]_D^{20}$ +30·0° (*l*, 2; *c*, 4·5 in $CHCl_3$), the inactive hydroperoxide being isolated.

(vii) sec.-*Butyl alcohol.* Reaction of the alcohol with hydrogen peroxide and concentrated sulphuric acid did not give a hydroperoxide.

(viii) 3 : 3-*Dimethylbutan*-2-*ol.* It was hoped that rearrangement of the carbon skeleton during reaction (Whitmore *et al.*, *J. Amer. Chem. Soc.*, 1933, **55**, 1107) with the consequent formation of the known 1 : 1 : 2-trimethylpropyl hydroperoxide (Criegee and Dietrich, *loc. cit.*) would afford evidence for the formation of a free carbonium ion in the transition state of reaction. However, from the sulphuric acid catalysed reaction, after 216 hr., including 46 hr.' stirring at room temperature, the alcohol (3·2 c.c. from 5 c.c.) was recovered, leaving only 0·085 g. of a residue, b. p. 54—54°/15 mm., which liberated iodine from potassium iodide. An attempt to prepare the *p*-nitrobenzoate of this residue (Criegee and Dietrich, *loc. cit.*) was unsuccessful.

Reaction between 85—90% *Hydrogen Peroxide and Carboxylic Esters.*—(i) 1 : 2 : 3 : 4-*Tetrahydro*-1-*naphthyl hydrogen phthalate.* From an initially homogeneous solution of the hydrogen phthalate (2·0 g.) in hydrogen peroxide (15 c.c.) containing sodium hydrogen carbonate (1·4 g., 2·5 mols.), an oil began to separate on the surface after 0·5 hr. After 22 hr., water (15 c.c.) was added; the oil was extracted with ether, the extract washed and dried (Na_2SO_4), and the solvent removed, yielding a solid (0·90 g.). Recrystallisation from light petroleum gave 1 : 2 : 3 : 4-tetrahydro-1-naphthyl hydroperoxide (0·50 g.), m. p. and mixed m. p. 56°. In a similar experiment, the optically active ester, $[\alpha]_D^{19}$ +11·1° (*l*, 2; *c*, 4·1 in $CHCl_3$), yielded the optically inactive hydroperoxide.

(ii) 1 : 2 : 3: 4-*Tetrahydro*-1-*naphthyl acetate.* After being stirred for 6 hr., a mixture of the acetate (1·0 g.), hydrogen peroxide (10 c.c.), and 98% formic acid (0·02 c.c.) was extracted with ether, the extract washed with sodium hydrogen carbonate solution and dried (Na_2SO_4), and the solvent removed. The reddish-yellow oil was extracted with boiling light petroleum, yielding 1 : 2 : 3 : 4-tetrahydro-1-naphthyl hydroperoxide (0·04 g.), m. p. 56°. The yield was low because of decomposition of the hydroperoxide by the formic and acetic acids.

(iii) *Diphenylmethyl hydrogen phthalate.* A water-cooled solution of the hydrogen phthalate (0·5 g.) in hydrogen peroxide (5 c.c.) containing sodium hydrogen carbonate (0·3 g., 2·5 mols.) was diluted with water after 48 hr.; an ethereal extract yielded diphenylmethyl hydroperoxide (0·15 g.), m. p. 51° (from light petroleum), undepressed on admixture with the hydroperoxide obtained from diphenylmethanol. After acidification of the aqueous residue with 50% hydrochloric acid, some unchanged ester (0·14 g.), m. p. 145—147°, was obtained.

(iv) 1-iso*Butyl*-1-*methylpropyl hydrogen phthalate.* After 16 hr., a solution of the hydrogen

phthalate (kindly supplied by Drs. Kenyon and Wadden), m. p. 61—63° (1 g.), in hydrogen peroxide (5 c.c.) containing sodium hydrogen carbonate (0·76 g., 2·5 mols.) was diluted with water (10 c.c.) and extracted with ether. The washed and dried extract yielded 1-*iso*butyl-1-methylpropyl hydroperoxide (0·04 g.), identified as the hydrogen perphthalate (0·02 g.), m. p. and mixed m. p. 86—88°. By acidification of the aqueous residue from the reaction, some ester (0·64 g.), m. p. 60—62°, was recovered.

(v) 1-*Phenylethyl hydrogen phthalate*. Reaction of the hydrogen phthalate with hydrogen peroxide (10 c.c.) containing sodium hydrogen carbonate (1·5 g., 2·5 mols.) for 24 hr. gave no hydroperoxide, and 90% of the ester was recovered.

(vi) *Methyl hydrogen phthalate and 2-octyl hydrogen phthalate*. Solutions of the sodium salts of these half-esters are not stable in concentrated hydrogen peroxide. However, if the reaction mixtures were diluted with water when the final violent stage seemed imminent, the original hydrogen phthalates could be recovered in about 70% yield. No other reaction products could be isolated.

Reaction between Hydrogen Peroxide and sec.-*Butyl Sodium Sulphate.*—*sec.*-Butyl sodium sulphate was prepared from the alcohol, sulphamic acid, and pyridine (Burwell and Holmquist, *J. Amer. Chem. Soc.*, 1949, **71**, 1769). After 18 hr., no organic material could be obtained by ethereal extraction of a solution of the sulphate (0·5 g.) and sodium hydrogen carbonate (0·48 g.) in 85—90% hydrogen peroxide. Similarly no *sec.*-butyl hydroperoxide could be isolated, after 18 hr., from a mixture of the sulphate (8·8 g.), 85—90% hydrogen peroxide (6 c.c.), and aqueous potassium hydroxide (2·8 g. in 7·2 c.c. of water).

Reaction between 85—90% *Hydrogen Peroxide and Olefins.*—(i) iso*Pent-2-ene*. A mixture of the olefin (5 c.c.), hydrogen peroxide (5 c.c.), and concentrated sulphuric acid (0·02 c.c.) was stirred for 6 hr. and set aside for 16 hr. Water was then added and the product extracted with light petroleum, yielding *tert.*-amyl hydroperoxide (1·29 g.), b. p. 63—64°/37·5 mm., n_D^{20} 1·4158, from which was prepared the hydrogen perphthalate, m. p. and mixed m. p. 88—90° (decomp.) (Found: equiv., 252. Calc. for $C_{13}H_{16}O_5$: equiv., 252). The constitution of the hydroperoxide was further confirmed by its reduction, by aqueous sodium sulphite, to the corresponding alcohol, characterised as *tert.*-amyl *p*-nitrobenzoate, m. p. and mixed m. p. 83—84°.

(ii) *The olefin derived from* 3 : 5-*dimethylhexan*-3-*ol*. The olefin (5 c.c.; probably the unknown 3 : 5-dimethylhex-2-ene), obtained by dehydration of the alcohol, was stirred for 5 hr. with hydrogen peroxide (5 c.c.) and concentrated sulphuric acid (0·05 c.c.). The organic layer yielded 1-*iso*butyl-1-methylpropyl hydroperoxide (0·35 g.), b. p. 43°/0·1 mm., n_D^{25} 1·4333, from which was prepared the hydrogen perphthalate, m. p. and mixed m. p. 85—87° (Found: equiv., 296. Calc. for $C_{16}H_{22}O_5$: equiv., 294). A viscous residue (3·8 g.), b. p. >60°/0·1 mm., similar to that obtained in the preparation of the hydroperoxide from the alcohol and giving a strongly positive peroxide reaction with acidified potassium iodide–starch paper, was also isolated. A longer reaction period (19 hr.) resulted in the formation of only this high-boiling residue, which is probably the product of acid decomposition of the hydroperoxide. An attempted larger-scale preparation (10 c.c. of olefin) resulted in violent decomposition after 4 hr.

(iii) cyclo*Hexene*. Only the olefin was recovered from the reaction of *cyclo*hexene with hydrogen peroxide and concentrated sulphuric acid.

The infra-red absorption spectra of some of these peroxides, determined by Dr. G. J. Minkoff, will be published elsewhere.

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315. *The Reactions of Fluorocarbon Radicals. Part IX.* Synthesis and Reactions of Pentafluoropropionic Acid.*

By R. N. Haszeldine and K. Leedham.

Interaction of pentafluoroidoethane and acetylene yields 3 : 3 : 4 : 4 : 4-pentafluoro-1-iodobut-1-ene, oxidised to pentafluoropropionic acid, from which the derivatives C_2F_5X [X = CO_2Na, CO_2K, CO_2Ag, CO_2Me, CO_2Et, $CO{\cdot}NH_2$, CN, COCl, $CO_2{\cdot}CH{:}CH_2$, $CH_2{\cdot}OH$, CHO, $CH(OH)_2$, $CH_2{\cdot}NH_2$, $CH_2{\cdot}NCO$, and $CO{\cdot}O{\cdot}CO{\cdot}C_2F_5$] have been prepared; their infra-red spectra are discussed. The decomposition of salts of perfluoro-carboxylic acids under a variety of conditions is considered.

The synthesis of pentafluoropropionic acid first recorded in *Nature* (1950, **166**, 192) and presented in abstract at the 120th Meeting, Amer. Chem. Soc., New York, 1951, is now reported in detail.

The synthesis described earlier (Emeléus and Haszeldine, *J.*, 1949, 2953) for pentafluoroiodoethane:

$$CHCl_3 \xrightarrow{SbF_3Cl_2} CHF_2Cl \xrightarrow{\text{Pyrolysis}} C_2F_4 \xrightarrow{I_2} CF_2I{\cdot}CF_2I \xrightarrow{IF_5} CF_3{\cdot}CF_2I$$

is readily applied on a larger scale and forms a convenient route to this compound. Reaction of the fluoro-iodide with acetylene under conditions favouring a free-radical chain reaction (Part VI, *J.*, 1952, 3483) gives a high yield of the addition compound (I), oxidation of which with alkaline potassium permanganate gives pentafluoropropionic acid:

$$C_2F_5I + C_2H_2 \xrightarrow[\text{or light}]{\text{Heat}} C_2F_5{\cdot}CH{:}CHI \xrightarrow{KMnO_4} C_2F_5{\cdot}CO_2H$$

(I)

This strong acid boils some 45° lower than propionic acid (141°), and is conveniently characterised by its infra-red spectrum or by the spectrum of the solid nitron pentafluoropropionate. Small amounts of the acid present in aqueous solution are readily detected and estimated as the nitron salt. A urea derivative could not be obtained by reaction with carbodi-imines (Part VI, *loc. cit.*).

Pentafluoropropionic acid may also be obtained by two alternative routes: electrolysis of propionyl fluoride in anhydrous hydrogen fluoride, followed by hydrolysis of the pentafluoropropionyl fluoride (Minnesota Mining and Manufacturing Co., personal communication), and carboxylation of pentafluoropropylmagnesium iodide ($C_2F_5I \longrightarrow C_2F_5{\cdot}MgI \longrightarrow C_2F_5{\cdot}CO_2H$; unpublished, this laboratory).

Sodium, potassium, and silver salts, methyl and ethyl esters, the amide, the nitrile, and the acid chloride were obtained by slight modification of standard techniques. Decomposition of salts of perfluoroalkanecarboxylic acids, $CF_3{\cdot}[CF_2]_n{\cdot}CO_2M$, can yield, depending on the conditions and on the nature of M, the hydrogeno-compound, $CF_3{\cdot}[CF_2]_n{\cdot}H$, the olefin, $CF_3{\cdot}[CF_2]_{n-2}{\cdot}CF{:}CF_2$, or the fluorocarbon, $CF_3{\cdot}[CF_2]_{2n}{\cdot}CF_3$, the last two reactions having no parallel in the hydrocarbon series. Aqueous solutions of sodium or potassium pentafluoropropionate, particularly if sodium or potassium hydroxide or carbonate is added, yield pentafluoropropane at 150—200°; decarboxylation is particularly efficient in boiling ethylene glycol. Pyrolysis (250°) of the anhydrous salts yields tetrafluoroethylene, carbon dioxide, and alkali-metal fluoride (Haszeldine, *J.*, 1952, 4259). It is believed that in both instances fluorocarbanion formation occurs, followed by rapid abstraction of hydrogen from the solvent or, where this is impossible, stabilisation by elimination to yield the olefin:

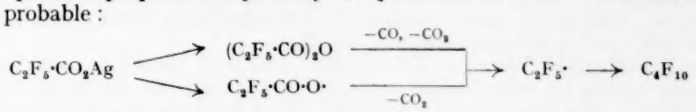
$$C_2F_5{\cdot}CO_2M \longrightarrow C_2F_5{\cdot}CO_2^- \longrightarrow CO_2 + C_2F_5^- \xrightarrow{\text{Solvent}} C_2F_5H$$

$$\downarrow \text{Elimination}$$

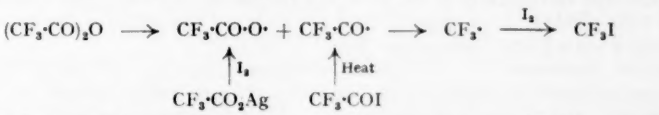
$$F^- + C_2F_4$$

* Part VIII, *J.*, 1953, 922.

(cf. the reactions of perfluoroalkyl Grignard reagents, *J.*, 1952, 3423). Aqueous solutions of silver pentafluoropropionate similarly yield pentafluoropropane at 200°, but when this salt is heated in the dry state at 300° perfluoro-*n*-butane (mainly) and perfluoropropionic anhydride are formed. Pyrolysis of silver heptafluorobutyrate similarly yields perfluoro-*n*-hexane (75—85%) and perfluorobutyric anhydride (10—20%). The anhydrides are possibly precursors of the fluorocarbons, since the yields of the former increase when the pyrolysis products are removed from the seat of reaction as rapidly as possible, and pyrolysis of perfluoropropionic anhydride yields perfluoro-*n*-butane. Free-radical mechanisms seem probable :



It was shown earlier that perfluoroacetic anhydride was obtained when silver trifluoroacetate was heated with phosphorus or sulphur, and that heating perfluoroacetic anhydride and iodine gave trifluoroiodomethane, also obtained by pyrolysis of trifluoroacetyl iodide or by interaction of iodine and silver trifluoroacetate (*J.*, 1951, 584; 1952, 4259).



Silver pentafluoropropionate, like silver trifluoroacetate and silver perchlorate, is readily soluble in ether and benzene.

Interaction of pentafluoropropionic acid and acetylene gave vinyl pentafluoropropionate, hydrogenation of which yielded ethyl pentafluoropropionate. Reduction of the acid with lithium aluminium hydride gave pentafluoropropanol and pentafluoropropaldehyde hydrate. Oxidation of the alcohol to pentafluoropropionic acid is difficult and is best effected by potassium permanganate. The aldehyde hydrate can be distilled without decomposition, and fails to yield a 2 : 4-dinitrophenylhydrazone unless a dehydrating agent, *e.g.*, sulphuric acid, is present. Treatment of the hydrate with phosphoric anhydride gave the volatile pentafluoropropaldehyde. Application of the lithium aluminium hydride technique to pentafluoropropionamide yielded pentafluoro-*n*-propylamine which, like trifluoroethylamine, gives a stable diazo-compound, $C_2F_5{\cdot}CHN_2$ and can be converted into the *iso*cyanate by reaction with carbonyl chloride.

X :	CO_2H	CO_2Me	CO_2Et	$CO{\cdot}NH_2$	
C.S. no.	14	15	16	17	
C_2F_5X	5·62 (5·48)	5·59	5·56	5·84	6·13
$CH_3{\cdot}[CH_2]_n{\cdot}X$	5·83	5·7—5·8	5·7—5·8	2 bands	5·9—6·2

X :	COCl	CHO	$CO{\cdot}O{\cdot}COC_2F_5$	
C.S. no.	18		19	
C_2F_5X	5·51	5·73	5·33	5·51
$CH_3{\cdot}[CH_2]_n{\cdot}X$	5·55—5·60	5·8—5·9	5·4—5·5 †	5·6—5·7 †

† For $(CH_3{\cdot}[CH_2]_n{\cdot}CO)_2O$.

The infra-red spectra of the derivatives * are more useful for identification than are their other physical properties. The carbonyl stretching absorptions shown in the Table reveal the strong inductive effect of the fluoro-group, since a marked shift to shorter wavelength of the " characteristic " vibration of the hydrocarbon analogues is apparent.

The amide N–H stretching vibrations are at 2·97 and 3·13 μ, and the C≡N stretching vibration appears at 4·41 μ (cf. $CH_3{\cdot}[CH_2]_{2n}{\cdot}CN$, 4·44 μ) (the spectrum of $C_2F_5{\cdot}CN$ has C.S. no. 20*). It is evident that correlation rules for the characteristic frequencies of specific groups in fluorocarbon derivatives can be drawn up, but will differ from the rules applicable to hydrocarbon derivatives, and will prove equally useful in qualitative analysis.

* Some of the spectra have been deposited with the Chemical Society (cf. *Proc.*, 1952, 164), and photocopies may be obtained from the General Secretary. Identifying C.S. numbers are listed in the Table and must be cited in requests for photocopies.

Experimental

Pentafluoroiodoethane.—To a stainless-steel autoclave (300 ml.) were added dry iodine (210 g., 0·83 mol.), α-pinene stabiliser (0·25 ml.), and tetrafluoroethylene (20 g., 0·2 mol.), air being excluded. After 24 hr. at the optimum temperature of 150°, the gaseous and the liquid products were pumped from the autoclave and after addition of a further 20 g. of tetrafluoroethylene the heating was repeated. Eighty grams of tetrafluoroethylene were thus treated without recharging with iodine. The maximum pressure was 30 atm. at 100°. At >150° or higher initial pressures of tetrafluoroethylene, cyclic dimerisation, polymerisation, and formation of carbon occur. Distillation gave tetrafluoro-1 : 2-di-iodoethane (200 g., 76%), tetrafluoroethylene (*ca.* 20%), and octafluoro*cyclo*butane (*ca.* 2%).

To iodine pentafluoride (700 g.) in a 2-l. nickel vessel with flanged top and nickel, reflux water-condenser leading *via* rubber tubing to traps cooled in liquid air, was added tetrafluorodi-iodoethane (10 g.). The temperature was slowly raised until reaction began (*ca.* 90°), and further tetrafluorodi-iodoethane (90 g.) was added dropwise during 5 hr., the temperature being kept at 90—100°. The reaction was thus readily controlled, and the yield of pentafluoroiodoethane, washed with aqueous alkali to remove traces of iodine, etc., was 85% (Found : *M*, 246. Calc. for C_2F_5I: *M*, 246) : this had b. p. 13°. Emeléus and Haszeldine (*loc. cit.*) report b. p. 13°.

Preparation and Oxidation of 3 : 3 : 4 : 4 : 4-*Pentafluoro*-1-*iodobut*-1-*ene.*—This material was prepared in 72% yield by interaction at 240° for 20 hr. of pentafluoroiodoethane (3·25 g.) and acetylene (0·41 g.) in a 30-ml. Carius tube (Part VI, *loc. cit.*).

In a typical experiment the pentafluoroiodobutene (20·8 g.) was added dropwise during 5 hr. to a stirred solution of potassium permanganate (62·4 g.) and potassium hydroxide (4·53 g.) in water (300 ml.), and the whole heated at 90°. After final heating at 120° for 1½ hr. droplets were no longer apparent in the condenser, and the solution was acidified (H_2SO_4), treated with sulphur dioxide, made alkaline (KOH), concentrated until potassium sulphate was deposited on cooling, filtered, acidified (H_2SO_4), and extracted with ether for 48 hr. The ethereal extracts were dried ($MgSO_4$) and distilled, to give an acid fraction, b. p. 109·5—110·5° (3·8 g.), which was exactly neutralised with 10% sodium carbonate solution. After evaporation to dryness, treatment with concentrated sulphuric acid and distillation from a trace of phosphoric anhydride gave *pentafluoropropionic acid* (22%), b. p. 95·5—95·7°, n_D° 1·298 (Found : C, 21·7%; Equiv., 163·6, 164·1. $C_3HO_2F_5$ requires C, 21·9%; Equiv., 164·0).

In a second experiment the order of addition was reversed, a hot solution of potassium permanganate (44·0 g.) and potassium hydroxide (2·0 g.) in water (250 ml.) being added during 1·5 hr. to 3 : 3 : 4 : 4 : 4-pentafluoro-1-iodobut-1-ene (9·4 g.) and sodium carbonate (2·0 g.) in water (25 ml.) at 90°. Unchanged olefin was not detected, and after acidification (H_2SO_4), ether-extraction (48 hr.), shaking with mercury to remove iodine, drying, and removal of the ether, followed by treatment as described above, pentafluoropropionic acid was obtained in 30% yield.

Volatile material liberated during the oxidation was shown to be pentafluoroethane (1·0 g.), b. p. −48° (Found : F, 78·2%; *M*, 122. Calc. for C_2HF_5 : F, 79·2%; *M*, 120). Young, Fukuhara, and Bigelow (*J. Amer. Chem. Soc.*, 1940, **62**, 1171) report b. p. −48·4°. Fluoride was liberated during the oxidation.

Pentafluoropropionic acid is a strong, hygroscopic acid which fumes in air and has an odour similar to that of heptafluorobutyric acid (Haszeldine, *J.*, 1950, 2789). It is readily soluble in water, ethanol, acetone, carbon tetrachloride, benzene, and ether.

A freshly prepared (6%) solution of nitron in aqueous acetic acid (10%) was slowly added to a solution of pentafluoropropionic acid in water, to give *nitron pentafluoropropionate* (Found : N, 11·8. $C_{23}H_{17}O_2N_4F_5$ requires N, 11·8%), m. p. 204—206° (decomp.) after recrystallisation from aqueous ethanol. The nitron salt is best characterised by its infra-red spectrum (C.S.21; see footnote, p. 1549).

Silver, Sodium, and Potassium Pentafluoropropionate.—Neutralisation of aqueous pentafluoropropionic acid with silver oxide or silver carbonate, and evaporation to dryness or extraction with ether followed by evaporation to dryness of the ethereal extracts, yielded colourless, crystalline silver pentafluoropropionate. When heated with an excess of iodine the silver salt gives pentafluoroiodoethane in high yield (Haszeldine, *J.*, 1952, 4259). When heated above its m. p. (245°) at atmospheric pressure silver pentafluoropropionate (2·1 g.) gave perfluoro-*n*-butane (85%), b. p. 1° (Found : *M*, 236. Calc. for C_4F_{10}: *M*, 238), and perfluoropropionic anhydride (10%) (see below). Fowler *et al.* (*Ind. Eng. Chem.*, 1947, **39**, 375) report b. p. −1·7° for perfluoro-*n*-butane. When the salt was heated in a nickel apparatus to

500°/0·1 mm. during 3 hr. the yields of perfluorobutane and anhydride were 74 and 20%. Traces of pentafluoropropionyl fluoride were also obtained.

Pyrolysis of silver heptafluorobutyrate (4·2 g.) (*J.*, 1950, 2789) at 550° during 5 hr. similarly yielded perfluoro-*n*-hexane (81%), b. p. 55—56° (Found : *M*, 335. Calc. for C_6F_{14} : *M*, 338), and perfluorobutyric anhydride (11%), b. p. 107° (Found : *M*, 409. Calc. for $C_8O_3F_{14}$: *M*, 410). Haszeldine (*J.*, 1952, 3423; 1950, 2789) reports b. p. 56° and 108° for these compounds. Pyrolysis *in vacuo* gave perfluorohexane (75%) and the anhydride (16%).

Neutralisation of an aqueous solution of pentafluoropropionic acid with potassium or sodium carbonate, followed by evaporation to dryness, purification by extraction with ethanol and evaporation to dryness of the ethanolic solution, gave *potassium pentafluoropropionate* (Found : K, 19·4. $C_3O_2F_5K$ requires K, 19·3%) and *sodium pentafluoropropionate* (Found : Na, 12·2. $C_3O_2F_5Na$ requires Na, 12·4%) as colourless crystals. Pyrolysis of thoroughly dried potassium pentafluoropropionate (2·2 g.) at 250° gave tetrafluoroethylene (80%) (Found : *M*, 100. Calc. for C_2F_4 : *M*, 100) (identified spectroscopically), potassium fluoride, carbon dioxide, and a small amount of carbon.

Ethyl and Methyl Pentafluoropropionate.—Pentafluoropropionic acid (4·80 g.), ethyl alcohol (1·2 g.), and concentrated sulphuric acid (0·2 ml.) were set aside for 8 hr. at room temperature, then heated under reflux for 3 hr. After rapid washing with ice-water and drying (P_2O_5), distillation gave *ethyl pentafluoropropionate* (4·46 g., 79%), b. p. 76·5°/773 mm., n_D^{22} 1·300, (Found : C, 31·6; H, 3·0. $C_5H_5O_2F_5$ requires C, 31·2; H, 2·6%).

Methanol similarly gave *methyl pentafluoropropionate* (85%), b. p. 60·5°, n_D^{12} 1·295 (Found : C, 28·3%; *M*, 180. $C_4H_3O_2F_5$ requires C, 27·6%; *M*, 178).

Pentafluoropropionamide and Pentafluoropropionitrile.—Through an ice-cold ethereal solution of ethyl pentafluoropropionate (2·0 g.) was passed an excess of dry ammonia. Evaporation of the ether followed by sublimation of the residual solid at 60°/760 mm. gave *pentafluoropropionamide* (1·5 g., 88%), m. p. 96° (Found : C, 22·3; H, 1·7; N, 8·7. $C_3H_2F_5ON$ requires C, 22·1; H, 1·2; N, 8·6%).

The amide (1·75 g.), mixed with an excess of phosphoric anhydride (5 g.), was heated under a reflux air-condenser connected to a trap cooled by liquid oxygen. After 30 min.' heating the amide which had sublimed was returned to the reaction vessel with a further quantity of phosphoric anhydride (5 g.). After re-heating, fractionation of the volatile products gave *pentafluoropropionitrile* (1·0 g.), b. p. −35° (Found : C, 23·9%; *M*, 145. C_3NF_5 requires C, 24·8%; *M*, 145).

Pentafluoropropionyl Chloride.—Benzoyl chloride (6·43 g.) and pentafluoropropionic acid (3·11 g.) were heated under reflux at 150° during 7 hr. to give, as volatile product, *pentafluoropropionyl chloride* (2·82 g., 82%), b. p. 9·4° (Found : C, 19·2; Cl, 19·4%; *M*, 182·5. C_3OClF_5 requires C, 19·7; Cl, 19·45%; *M*, 182·5), purified by fractionation *in vacuo*.

Vinyl Pentafluoropropionate.—Pentafluoropropionic acid (1·9 g.), sealed with its sodium salt (0·2 g.) and an excess of acetylene in a Pyrex tube and heated at 220—240° for 12 hr., gave *vinyl pentafluoropropionate* (75%), b. p. 60°, n_D^{20} 1·310 (Found : C, 31·8; H, 2·2%; *M*, 190. $C_5H_3O_2F_5$ requires C, 31·6; H, 1·6%; *M*, 190).

Pentafluoropropaldehyde and Pentafluoropropanol.—To an ice-cold solution of lithium aluminium hydride (0·5 g.) in dry ether (15 ml.) was added pentafluoropropionic acid (1·8 g.) in ether (10 ml.) during 45 min. After 30 min.' stirring, sulphuric acid (2 ml. of concentrated acid in 5 ml. of water) was carefully added and, after separation of the ether, and extraction of the aqueous layer with ether (10 ml.), the combined ethereal extracts were distilled to give a fraction, b. p. 78—82°, which, on redistillation from phosphoric anhydride, gave *pentafluoropropanol* (38%), b. p. 81°, n_D^{15} 1·295 (Found : C, 24·0. $C_3H_3OF_5$ requires C, 24·0%), and a fraction, b. p. 87—105°, which was taken up in ether and dried ($MgSO_4$). Distillation of the ethereal solution gave the *propaldehyde hydrate* (32%), b. p. 92—94°, m. p. 54—56° (Found: C, 21·7; H, 2·0. $C_3H_3O_2F_5$ requires C, 21·7; H, 1·8%), treatment of which with phosphoric anhydride, followed by fractionation *in vacuo*, gave *pentafluoropropaldehyde* (27% overall yield), b. p. 3·5° (Found : C, 24·1%; *M*, 147. C_2HOF_5 requires C, 24·3%; *M*, 148). The 2 : 4-*dinitrophenylhydrazone* had m. p. 129—130° (Found : N, 17·0. $C_9H_5O_4N_4F_5$ requires N, 17·1%).

*Pentafluoro-*n*-propylamine.*—Treatment of a solution of pentafluoropropionamide (2·6 g.) with lithium aluminium hydride (0·5 g.) by the method given above, but with dibutyl ether in place of diethyl ether, gave, after distillation of the ethereal extracts from calcium oxide, *pentafluoro-*n*-propylamine* (81%), b. p. 51°, n_D^{15} 1·300 (Found : 9·1%; *M*, 149. $C_3H_4NF_5$ requires N, 9·4%; *M*, 149). The amine (1·9 g.) was sealed with carbonyl chloride (10% excess) and perfluoro-1 : 3 : 5-trimethyl*cyclo*hexane (as inert medium) and heated to 100° for 2 hr., to give

2 : 2 : 3 : 3 : 3-*pentafluoropropyl* isocyanate (63%), b. p. 74·5°, n_D^{20} 1·339 (Found: N, 8·0%; *M*, 173. $C_4H_2NOF_5$ requires N, 8·0%; *M*, 175).

Perfluoropropionic Anhydride.—Pentafluoropropionic acid (2·2 g.), heated with an excess of phosphoric anhydride to 200° for 24 hr., gave *perfluoropropionic anhydride* (88%), b. p. 68° (Found: C, 23·1%; *M*, 306. $C_6O_3F_{10}$ requires C, 23·2%; *M*, 310).

Pyrolysis of the anhydride at 350° in a platinum-lined tube yielded perfluoro-*n*-butane (65%), carbon dioxide and monoxide, and unchanged anhydride (20%).

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316. *Organometallic and Organometalloidal Fluorine Compounds. Part VI.* Trifluoromethyl Arsenicals.†*

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The compounds $(CF_3)_3As$, $(CF_3)_2AsI$, and $CF_3{\cdot}AsI_2$ have been used to prepare $(CF_3)_2AsX$, $CF_3{\cdot}AsX_2$, $(CF_3)_3AsX_2$ (X = Br, Cl, F, CN, SCN), and $[(CF_3)_2As]_2O$. The hydrolysis of these compounds and of the hydrides $(CF_3)_2AsH$ and CF_3AsH_2 (which are also prepared) has been studied, and an explanation is advanced to account for the unusual results.

A novel type of exchange reaction involving the replacement of trifluoromethyl by methyl groups in tristrifluoromethylarsine is described and has been used to obtain $(CF_3)_2AsMe$, independently synthesised from $(CF_3)_2AsI$. Oxidative hydrolysis of the iodo-compound yields the strong, monobasic bistrifluoromethylarsinic acid. Ultra-violet and infra-red data for a variety of trifluoromethyl arsenicals are discussed.

INTERACTION of arsenic and trifluoroiodomethane yields tristrifluoromethylarsine, iodobistrifluoromethylarsine, di-iodotrifluoromethylarsine, and arsenic tri-iodide (Part V, *loc. cit.*; Walaschewski, forthcoming publication). There is now evidence that a series of equilibria is set up in this reaction. Thus, when iodobistrifluoromethylarsine is heated alone, trifluoroiodomethane and tristrifluoromethylarsine are the main products, and small amounts of arsenic, arsenic tri-iodide, and di-iodotrifluoromethylarsine are also detected; similarly, di-iodotrifluoromethylarsine yields arsenic tri-iodide and tristrifluoromethylarsine. Under similar conditions, tristrifluoromethylarsine reacts with arsenic tri-iodide to give the iodotrifluoromethylarsines, trifluoroiodomethane, and arsenic:

$$2(CF_3)_2AsI \rightleftharpoons (CF_3)_3As + CF_3{\cdot}AsI_2$$
$$2CF_3{\cdot}AsI_2 \rightleftharpoons (CF_3)_2AsI + AsI_3$$
$$(CF_3)_3As + AsI_3 \rightleftharpoons (CF_3)_2AsI,\ CF_3AsI_2,\ CF_2I,\ As,\ \text{etc.}$$

At equilibrium, under optimum conditions, the yields of the iodotrifluoromethylarsines obtained by the reaction of arsenic with trifluoroiodomethane are low, but may be increased by the use of a mixture of arsenic and arsenic tri-iodide (see Experimental section).

The iodotrifluoromethylarsines have been used to synthesise the compounds $CF_3{\cdot}AsCl_2$, $(CF_3)_2As{\cdot}O{\cdot}As(CF_3)_2$, $(CF_3)_2As{\cdot}As(CF_3)_2$, and $(CF_3)_2AsX$ (X = F, Cl, CN, SCN, OCN) by reaction with the appropriate silver or mercury salts (Part V; Walaschewski *loc. cit.*). The iodides have also been reduced to the hydrides, trifluoromethylarsine and bistrifluoromethylarsine, by use of lithium aluminium hydride or, preferably, zinc and hydrochloric acid. It is noteworthy that lithium aluminium hydride did not affect the trifluoromethyl groups and that trifluoromethylarsine was formed quantitatively by use of zinc and hydro-

* Part V, Brandt, Emeléus, and Haszeldine, *J.*, 1952, 2582.
† Presented in abstract at XIIth International Congress, New York, 1951.

chloric acid. Thermal decomposition of bistrifluoromethylarsine (b. p. 19°), which is appreciably more stable than arsine, proceeds according to the equation :

$$3(CF_3)_2AsH \longrightarrow (CF_3)_3As + 2As + 3CF_3H$$

Trifluoromethylarsine similarly yielded arsenic, hydrogen, and fluoroform, but no tristrifluoromethylarsine. In neither case was hexafluoroethane formed, and this suggests that the decomposition does not involve free trifluoromethyl radicals, and that some disproportionation of bistrifluoromethylarsine to tristrifluoromethylarsine and trifluoromethylarsine occurs as the first step.

The hydrolysis of the trifluoromethylarsines is discussed below. Detection of the trifluoromethylarsines is best effected by their infra-red spectra. The As–H stretching vibration appears at 4·67 μ in $(CF_3)_2AsH$ and at 4·71 μ in $CF_3{\cdot}AsH_2$, the intensity being appreciably greater for the latter. Robertson and Fox (*Proc. Roy. Soc.*, **1928**, *A*, **120**, 161) report 4·71 μ for the As–H vibration in arsine, so replacement of two of the hydrogen atoms in arsine by trifluoromethyl groups causes a shift to shorter wave-length. The weaker bands at 4·45 μ are ascribed to overtones and combination frequencies of the strong C–F stretching absorptions at 8—9 μ.

Tristrifluoromethylarsine shows only end-absorption in the ultra-violet and, by comparison with trifluoromethylarsine, replacement of hydrogen by trifluoromethyl causes

TABLE 1.

	λ 250	240	230	220
$CF_3{\cdot}AsH_2$ vapour	ε 0·21	0·88	2·07	7·75
$(CF_3)_3As$ vapour	ε 1·89	6·75	12·6	18·7

appreciable increase in absorption (Table 1). The chromophoric effect of the As–As bond is revealed by the spectrum of tetrakistrifluoromethyldiarsine ($\lambda_{max.}$ 223 mμ; ε 3000).

In Table 2 the effect of replacement of an iodine atom by a trifluoromethyl group on the ultra-violet spectrum of arsenic tri-iodide is shown. The long-wave-length maximum of the tri-iodide becomes an inflection in di-iodotrifluoromethylarsine with considerable shift to shorter wave-length, whereas the 280-mμ maximum moves to 271 mμ in the di-iodide and to 290 mμ in the monoiodide. The shifts to shorter wave-length are analogous

TABLE 2.

	Solvent *	$\lambda_{max.}$	$\varepsilon_{max.}$	$\lambda_{min.}$	$\varepsilon_{min.}$	$\lambda_{infl.}$	$\varepsilon_{infl.}$
AsI_3	Pet.	378	1,600	350	750	—	—
		280	5,600	261	2,900	—	—
		225	12,000	—	—	—	—
CF_3AsI_2	Pet.	271	4,200	252	3,100	325	1,700
		229	6,500	219	5,600	—	—
	Ether	267	4,000	254	3,800	326	1,500
		230	5,500	220	5,000	—	—
$(CF_3)_2AsI$	Vapour	290	—	248	—	—	—
	Pet.	290	1,200	255	350	—	—
	Ether	287	1,200	256	500	—	—

* Pet. = light petroleum (b. p. 60—80°).

to those observed for methyl and trifluoromethyl sulphur compounds (Brandt, Emeléus, and Haszeldine, *J.*, 1952, 2549). The effect of solvent is negligible, ether producing only the usual slight shift relative to light petroleum or to the vapour.

Attempts were made to prepare trifluoromethyl- and bistrifluoromethyl-arsine from tristrifluoromethylarsine and hydrogen. Fluoroform and arsenic were the only products from the thermal reaction, but the conditions necessary to effect reaction were such that thermal decomposition of the hydrides would have occurred. Exposure of a mixture of tristrifluoromethylarsine and hydrogen to ultra-violet light yielded a mixture of fluoroform (mainly) and hexafluoroethane. Photochemical decomposition of tristrifluoromethylarsine alone yields arsenic and hexafluoroethane, but since the number of trifluoromethyl radicals present at any one instant is small, it is not surprising that when hydrogen is present reaction (*a*) occurs in preference to (*b*). The arsines $CF_3{\cdot}AsH_2$ and $(CF_3)_2AsH$ were not detected by infra-red spectroscopic examination, thus indicating that a reaction

of type (*c*) does not occur, or that the trifluoromethyl arsines are decomposed by light much faster than tristrifluoromethylarsine.

$$CF_3\cdot + H_2 \longrightarrow CHF_3 + H\cdot \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (a)$$

$$CF_3\cdot + CF_3\cdot \longrightarrow C_2F_6 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (b)$$

$$(CF_3)_2As\cdot + H_2 \longrightarrow (CF_3)_2AsH + H\cdot \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (c)$$

A novel type of radical-exchange reaction occurred when tristrifluoromethylarsine and methyl iodide were exposed to ultra-violet light, and products of the type $(CF_3)_n(CH_3)_{3-n}As$ were produced, as well as trifluoroiodomethane and hexafluoroethane. The main product, methylbistrifluoromethylarsine, could not be separated from tristrifluoromethylarsine by distillation, but was detected by its infra-red spectrum. Treatment of the mixture with aqueous sodium hydroxide removed the tristrifluoromethylarsine preferentially, since methylbistrifluoromethylarsine is only slowly hydrolysed by this reagent (see below). Small amounts of trimethylarsine and possibly dimethyltrifluoromethylarsine formed by the exchange reaction were removed by compound formation with mercuric chloride; methylbistrifluoromethylarsine, like tristrifluoromethylarsine, fails to react with mercuric chloride. The identity of the methylbistrifluoromethylarsine obtained by the exchange reaction was confirmed by its synthesis from iodobistrifluoromethylarsine and methyl magnesium iodide: $(CF_3)_2AsI + CH_3MgI \longrightarrow (CF_3)_2AsCH_3 + MgI_2$. The successful application of this synthesis opens up a route for the preparation of a wide variety of mixed perfluoroalkyl–alkyl- or –aryl-arsenicals. The infra-red spectrum of methylbistrifluoromethylarsine (b. p. 52°) enables it to be distinguished from tristrifluoromethylarsine (b. p. 33°) more easily than by its boiling point, which is somewhat higher than that of trimethylarsine (b. p. 49·5°), again illustrating the increase in boiling point on replacement of only a few atoms of hydrogen in a compound by fluorine. In particular the infra-red spectrum shows C–H bands at 3·40, 3·50, 7·03, and 7·25 μ due to the methyl group, and the pattern of the C–F bands at 8·5—9·0 μ shows its similarity to tetrakistrifluoromethyldiarsine which also contains the $(CF_3)_2As$ group.

The mechanism of the photochemical reaction of tristrifluoromethylarsine with methyl iodide is not yet clear. The influence of the strongly electronegative trifluoromethyl groups in this arsine is made apparent by its failure to form compounds with mercuric chloride or sulphur. Quaternary-salt formation was not observed with tristrifluoromethylarsine and trifluoroiodomethane even at 200°, again illustrating the resistance of the carbon–iodine bond in trifluoroiodomethane to heterolytic fission (cf. Banus, Emeléus, and Haszeldine, *J.*, 1951, 60). Methyl iodide readily forms quaternary salts with trialkylarsines, but is substantially immiscible with tristrifluoromethylarsine at, or below, room temperature and fails to react even at 140°. At 235°, however, the reaction is similar to that brought about by light, and yields trifluoroiodomethane, fluoroform, methylbistrifluoromethylarsine, and a mixture of methyltrifluoromethyl- and bistrifluoromethyliodoarsines. A stable quaternary salt of methyl iodide and tristrifluoromethylarsine could not be isolated, but it is probable that this is the intermediate in the exchange reaction:

$$(CF_3)_3As + CH_3I \xrightarrow[\text{or heat}]{h\nu} \left[(CF_3)_3As{<}^{Me}_{I}\right] \longrightarrow (CF_3)_2As\cdot CH_3 + CF_3I$$

Since methyl radicals will be produced rather than trifluoromethyl radicals under the conditions used, a simple radical mechanism would be:

$$CH_3I \xrightarrow[\text{or heat}]{h\nu} CH_3\cdot + \cdot I$$

$$CH_3\cdot + (CF_3)_3As \longrightarrow (CF_3)_2As\cdot CH_3 + CF_3\cdot$$

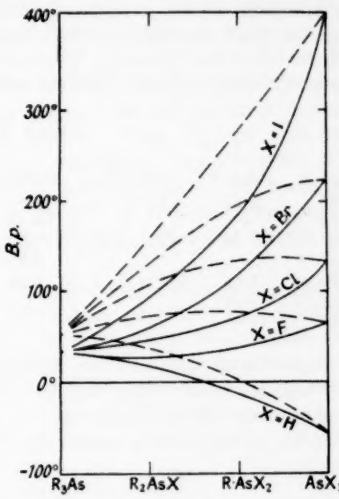
$$CF_3\cdot + I\cdot \longrightarrow CF_3I, \text{ etc.}$$

but although this would account for the formation of hexafluoroethane (radical combination) and fluoroform (hydrogen abstraction), it might be expected that other products, *e.g.*, methane or 1 : 1 : 1-trifluoroethane, arising from the known reactions of methyl or trifluoromethyl radicals in the presence of hydrogen-containing compounds, would have been observed. The absence of tetramethylarsonium iodide shows that the

methyl iodide reacts completely in the initial stages, and is not available for combination with the trimethylarsine produced in the later stages of the reaction.

The scope and mechanism of this radical-exchange reaction, which may be of general application, are being investigated.

Tristrifluoromethylarsine is the main product from the interaction of arsenic and trifluoroiodomethane, and its conversion into other compounds of use in further syntheses has been investigated. When heated with chlorine, tristrifluoromethylarsine is converted quantitatively into chlorotrifluoromethane and arsenic trichloride. If the reaction is carried out in the liquid phase at room temperature, however, smooth conversion into the quinquevalent derivative, $(CF_3)_3AsCl_2$, occurs. This compound, b. p. 98·5°, can be distilled without decomposition, but on prolonged heating at 125° decomposes to chlorotrifluoromethane, tristrifluoromethylarsine, chlorobistrifluoromethylarsine, dichlorotrifluoromethylarsine, and arsenic trichloride. Tristrifluoromethylarsenic dichloride is reconverted into tristrifluoromethylarsine by reaction with mercury at room temperature. Reaction of tristrifluoromethylarsine with chlorine in a small sealed tube for a long period at 15° yielded bistrifluoromethylarsenic trichloride and chlorotrifluoromethane. The



Boiling points of methyl- and trifluoromethyl-substituted arsines.

Broken lines: R = CH_3; solid lines: R = CF_3.

interaction of chlorine and tristrifluoromethylarsine in the vapour phase followed a different course and gave chlorotrifluoromethane, arsenic trichloride, and chlorotrifluoromethylarsine, but not the quinquevalent arsenic compounds. Thus, by suitable adjustment of reaction conditions, the compounds $(CF_3)_2AsCl$, CF_3AsCl_2, $(CF_3)_3AsCl_2$, or $(CF_3)_2AsCl_3$ can readily be prepared.

No evidence was obtained for the intermediate formation of tristrifluoromethylarsenic dibromide from tristrifluoromethylarsine and bromine; at −5° arsenic tribromide was deposited and bromotrifluoromethane evolved, and distillation of the residual liquid gave bromobistrifluoromethylarsine and dibromotrifluoromethylarsine. Although a solution of iodine in tristrifluoromethylarsine was slowly decolorised at room temperature, appreciable reaction occurred only at 100°. There was no evidence for the formation of a quinquevalent compound, and the products were iodobistrifluoromethylarsine, di-iodotrifluoromethylarsine, trifluoroiodomethane, and arsenic tri-iodide. Quantities of the iodotrifluoromethylarsines of value for further synthetic work may thus be prepared from tristrifluoromethylarsine.

Attempts to prepare tristrifluoromethylarsenic difluoride from tristrifluoromethylarsine and fluorine diluted by nitrogen, at temperatures between −100° and −20°, were unsuccessful. Carbon–arsenic bond fission occurred preferentially, as it did when tristrifluoromethylarsine was passed over cobalt trifluoride, and fluorobistrifluoromethyl-

arsine and probably difluorotrifluoromethylarsine were obtained. Tristrifluoromethylarsenic difluoride was successfully prepared, however, by the interaction of silver fluoride and tristrifluoromethylarsenic dichloride at room temperature; it can be distilled at atmospheric pressure; like the corresponding dichloride, it was converted by mercury into tristrifluoromethylarsine. It was apparent during the distillation of the several halogenotrifluoromethylarsines, that the order of thermal stability is As–F > As–Cl > As–Br > As–I. There is a systematic variation in the boiling points of the derivatives CF_3AsX_2, $(CF_3)_2AsX$ (X = F, Cl, Br, I, H) relative to the parent compounds $As(CF_3)_3$ and AsX_3. This is illustrated by the Figure where comparison with the corresponding methyl analogues is also made. It will be noted that the trifluoromethyl compounds invariably boil lower than their methyl analogues. The boiling points of the following unknown or uncharacterised compounds can be estimated from the diagram: $CF_3{\cdot}AsF_2$, 24°; $(CH_3)_2AsF$, 72°; $CH_3{\cdot}AsBr_2$, 200°; $CH_3{\cdot}AsI_2$, 275°.

The infra-red spectra of a series of compounds $CF_3{\cdot}AsX_2$ and $(CF_3)_2AsX$, and of $(CF_3)_3AsCl_2$, $(CF_3)_3As$, and $[(CF_3)_2As]_2$, have proved most useful for identification and analysis of mixtures. Examination reveals that the $CF_3{\cdot}AsX_2$ compounds (X = Cl, I, or H) are closely similar in the pattern of their C–F stretching vibrations in the 8—9-μ region, showing one main maximum, often broad, whose position depends on the nature of X: 8·95 μ (X = Cl), 9·14 μ (X = I), 8·80 μ (X = H). Compounds $(CF_3)_2AsX$ show two main C–F absorption bands, *A* and *B*, between 8 and 9·5 μ, *A* being broad with sub-maxima

TABLE 3.

X in $(CF_3)_2AsX$	Band *A*	Band *B*	X in $(CF_3)_2AsX$	Band *A*	Band *B*	X in $(CF_3)_2AsX$	Band *A*	Band *B*
Cl	8·45	9·13	H.....	8·44	8·97	CH_3	8·50	8·90
	8·85	—		8·58	—		8·64	9·03
I	8·5	9·20	CN	8·6	9·18	$As(CF_3)_2$ ...	8·54	9·04
	8·9	—		8·8	—		8·65	—
F	8·26	9·72	SCN	8·86	9·12	CF_3	8·25	9·04
	8·63	9·46					8·53	—
	8·85	—					8·70	—

(Table 3). Overtone and combination frequencies lie at 4·4—4·5 μ. The As–C and As–X vibrations usually lie at wave-lengths >15 μ.

The infra-red spectra* of all the arsenic compounds so far studied show a strong band *ca.* 13·6 μ (Table 4). This band is probably a CF_3 deformation frequency although it is

TABLE 4.

C.S. no.		μ	C.S. no.		μ	C.S. no.		μ
22	$(CF_3)_3As$	13·59		$(CF_3)_2As{\cdot}SCN$ ...	13·67	31	$CF_3{\cdot}AsCl_2$	13·69
23	$(CF_3)_2AsI$ ...	13·70	27	$(CF_3)_2As{\cdot}CN$ ...	13·62	32	$CF_3{\cdot}AsH_2$	13·66
24	$(CF_3)_2AsCl$ ...	13·66	28	$(CF_3)_2As{\cdot}CH_3$ ...	13·70	33	$(CF_3)_3AsCl_2$	13·42
25	$(CF_3)_2AsF$ ...	13·62	29	$[(CF_3)_2As]_2$	13·62	34	$(CF_3)_2AsO_2H$ ...	13·54
26	$(CF_3)_2AsH$ ...	13·65	30	$CF_3{\cdot}AsI_2$	13·75			

possible that it is the C–As stretching vibration moved to shorter wave-length by the influence of the trifluoromethyl groups, as observed for other fluorine compounds (Haszeldine, *Nature*, 1951, **168**, 1028).

Hydrolysis of Trifluoromethyl Arsenicals.—When the results described in the present communication are combined with those from Part V (*loc. cit.*), it is now seen that the following compounds liberate fluoroform rapidly and quantitatively on treatment with aqueous base: $As(CF_3)_3$, $(CF_3)_2AsX$ (X = F, Cl, Br, I, CN, or SCN), CF_3AsX_2 (X = Cl, Br, or I), $(CF_3)_3AsX_2$ (X = F or Cl), and $(CF_3)_2As{\cdot}O{\cdot}As(CF_3)_2$. The electronegative trifluoromethyl groups doubtless make the arsenic more susceptible to nucleophilic attack, and this is illustrated by the very marked decrease in rate of reaction when a trifluoromethyl group in tristrifluoromethylarsine is replaced by a methyl group. Thus, whereas

* Some of the spectra have been deposited with the Chemical Society (cf. *Proc.*, 1952, 164), and photocopies may be obtained from the General Secretary. Identifying C.S. numbers are listed in the Table and must be cited in requests for photocopies.

the reaction with tristrifluoromethylarsine is complete in 5—10 min., that with methylbistrifluoromethylarsine is incomplete with 20% sodium hydroxide solution even at 100°. Fluoroform, but no fluoride, is produced :

$$(CF_3)_2As{\cdot}CH_3 \xrightarrow{2NaOH} CH_3{\cdot}As(OH)_2 + 2CHF_3$$

Tetrakistrifluoromethyldiarsine was shown in Part V (*loc. cit.*) to undergo hydrolysis to both fluoroform and fluoride. The mechanism of this hydrolysis, which involves destruction under mild conditions of the normally stable trifluoromethyl group, has been studied further. The proportion of the trifluoromethyl groups appearing as fluoroform varies slightly according to the reaction conditions, but by use of a standard procedure 84% of the trifluoromethyl groups in tetrakistrifluoromethyldiarsine were converted into fluoroform and 16% into fluoride (and carbonate). The suggested mechanism (Part V) involves hydrolytic fission of the As–As bond :

$$(CF_3)_2As{\cdot}As(CF_3)_2 \xrightarrow{H_2O} (CF_3)_2AsH + (CF_3)_2As{\cdot}OH$$

Evidence given below shows that bistrifluoromethylarsinous acid decomposes in acid, neutral, or basic solution with the liberation of its trifluoromethyl groups as fluoroform. Study of bistrifluoromethylarsine, independently prepared as described above, shows that, under the standard conditions used for tetrakistrifluoromethyldiarsine, hydrolysis to fluoroform, fluoride, and carbonate occurs, 66% of the trifluoromethyl groups appearing as fluoroform and 34% as fluoride and carbonate. Thus, by the postulated mechanism, 1 mole of the diarsenic compound would be expected to give 2 moles of fluoroform from $(CF_3)_2As{\cdot}OH$ and $\frac{2}{3} \times 2$ moles from $(CF_3)_2AsH$, a total of $3\frac{1}{3}$ mole, *i.e.*, a *theoretical* conversion of 83% of the trifluoromethyl groups of tetrakistrifluoromethyldiarsine into fluoroform. The excellent agreement with the 84% found experimentally thus supports the suggested mechanism.

The reason for the instability of bistrifluoromethylarsine is not yet clear. Trifluoromethylarsine under similar conditions is also decomposed to give fluoroform (12—14%), fluoride, and carbonate, but appreciably less fluoroform is obtained as the number of hydrogen atoms attached to the arsenic increases. Other evidence is available which suggests that the analogous group $CF_2{\cdot}NH_2$ is unstable in basic solution. The disproportionation of trifluoromethylarsine to tristrifluoromethylarsine and arsine as an initial step of the hydrolysis can be excluded, since the absence of arsine was established by infra-red spectroscopy. As for bistrifluoromethylarsine, the ratio of fluoride to fluoroform varies slightly with the experimental conditions.

The hydrolysis of trifluoromethylarsine involves formation of *ca.* 15% of an unidentified bright yellow amorphous solid, which is also formed in small amount from bistrifluoromethylarsine, and in very small amount from tetrakistrifluoromethyldiarsine. The solid contains As^{III} and As^{V}, and is mainly arsenic, although a small percentage of a trifluoromethyl-containing compound can be detected by infra-red spectroscopic examination. After treatment with nitric acid, arsenic and fluoride can be estimated in the usual way. It is suggested that the solid is a compound, or mixture, of trifluoromethylarsine and arsenic. An analogous yellow powder formed by the decomposition of diphosphine, and as by-product involving other phosphorus hydrides, has formula P_2H according to Schenk (*Ber.*, 1903, **36**, 991, 4202), although the more recent work of Royen (*Z. anorg. Chem.*, 1936, **229**, 369) indicates that it is phosphine adsorbed on amorphous phosphorus.

The compounds $(CF_3)_2AsI$, $(CF_3)_2AsCl$, $CF_3{\cdot}AsI_2$, and $CF_3{\cdot}AsCl_2$ are stable to water at room temperature, and when they are compared with the corresponding methyl compounds or with arsenic trichloride or tri-iodide a decrease in the ease of hydrolysis is apparent. This is analogous to the increased stability of chloro- or iodo-trifluoromethane relative to methyl chloride or iodide. The first stage in the hydrolysis of the compounds $(CF_3)_2AsX$ (X = Cl, I, etc.) is presumably

$$OH^- + As(CF_3)_2{-}I \longrightarrow (CF_3)_2As{\cdot}OH + I^-$$

followed by further attack on the bistrifluoromethylarsinous acid. The electronegative trifluoromethyl groups facilitate nucleophilic attack on arsenic, but not the loss of iodine as an anion. Attempts to prepare bistrifluoromethylarsinous acid by stepwise hydrolysis of tristrifluoromethylarsine have been unsuccessful. This arsine is stable to water, but hydrolysis, which is fast in a buffer solution at pH 9·3, can still be detected at pH 7·2. If 85% of the sodium hydroxide theoretically required for removal of *one* trifluoromethyl group from tristrifluoromethylarsine is used, all three trifluoromethyl groups are lost. Since 15% of the tristrifluoromethylarsine remains, and since tristrifluoromethylarsine is substantially stable to hot concentrated acid, it follows (*a*) that hydroxide ion is essential to bring about hydrolysis, and that when it is used up hydrolysis ceases, and (*b*) that bistrifluoromethylarsinous acid is unstable in water:

$$(CF_3)_3As \xrightarrow{OH^-} (CF_3)_2As{\cdot}OH + CHF_3 \xrightarrow{2H_2O} NaH_2AsO_3 + 3CHF_3$$

and stepwise hydrolysis cannot be achieved.

Cyanobistrifluoromethylarsine is the only compound which can be hydrolysed by water, as distinct from alkali, and yields fluoroform and hydrogen cyanide. This also illustrates the instability of bistrifluoromethylarsinous acid:

$$(CF_3)_2As{\cdot}CN \xrightarrow{H_2O} (CF_3)_2As{\cdot}OH + HCN \xrightarrow{2H_2O} 2CHF_3 + HCN + H_3AsO_3$$

The silver salt of bistrifluoromethylarsinous acid was obtained by reaction of the monoiodo-compound with moist silver oxide, but, on liberation of the acid by hydrogen sulphide, potassium iodide or cyanide, etc., fluoroform was evolved. Mercuric oxide similarly gave the mercuric salt.

Reaction of iodobistrifluoromethylarsine with aqueous hydrogen peroxide liberated iodine and gave bistrifluoromethylarsinic acid (hexafluorocacodylic acid) with the formation of only traces of fluoroform:

$$(CF_3)_2AsI \xrightarrow[H_2O_2]{H_2O-} (CF_3)_2AsO_2H$$

The acid, purified by recrystallisation from chloroform or by sublimation, liberated fluoroform quantitatively on treatment with an excess of base, but was stable in aqueous solution; cold concentrated hydriodic or sulphuric acid had no effect. Hexafluorocacodylic acid forms a monosilver salt which is readily soluble in water and so prevents titration of the acid with aqueous silver nitrate. The infra-red spectra of bistrifluoromethylarsinic acid and its silver salt show C–F absorption at 8—9 μ and weak broad bands at 4·3 and 4·4 μ which can be distinguished from the C–F overtone bands. If these weak bands are ascribed to the As–OH stretching vibration, they indicate, without being decisive, that the acid exists in part as $(CF_3)_2As(OH)_3$, giving a silver salt $(CF_3)_2As(OH)_2(OAg)$ [cf. $(CF_3)_2AsO_2Ag$].

The molecular conductivity of an aqueous solution of bistrifluoromethylarsinic (hexafluorocacodylic) acid is 230 times as great as that of cacodylic acid at a dilution (l. mole^{-1}) of 32. The marked increase in acid strength so indicated is confirmed by titration with base. The hexafluoro-acid is a strong acid, comparable with hydrochloric and trifluoroacetic acid in aqueous solution, and is probably dibasic, since the first point of inflection on the titration curve is at pH 3·7; rapid titration with base at pH >7 gives some indication of a second point of inflection corresponding to $(CF_3)_2As(OH)(ONa)_2$. Cacodylic acid (K 4·2 $\times$ 10^{-7}) is an acid not much stronger than hydrogen sulphide. Hantzsch (*Ber.*, **1904**, **37**, 1076) from conductivity data postulated that cacodylic acid may be dibasic in strongly alkaline solution: $(CH_3)_2AsO_2H + 2NaOH \rightleftharpoons (CH_3)_2As(OH)(ONa)_2$. Replacement of methyl by trifluoromethyl will increase the tendency to react as a dibasic or possibly even as a tribasic acid. The very large increase in acid strength of the hexafluoro-acid again illustrates the powerful inductive effect of the trifluoromethyl group.

Experimental

Preparation of Tristrifluoromethylarsine, Iodobistrifluoromethylarsine, and Di-iodotrifluoromethylarsine.—Arsenic powder (100 g.) was mixed with broken porcelain (to prevent sintering to a solid mass and to give maximum surface area), and heated to 220° for 18—24 hr. in a stainless-steel autoclave (100-ml. capacity) with trifluoroiodomethane (40 g.). The trifluoromethylarsenic compounds were removed by pumping and fresh trifluoroiodomethane inserted for repeat preparations, made without emptying of the autoclave. The products, containing maximum yields of the iodo-compounds, were tristrifluoromethylarsine (78%), iodobistrifluoromethylarsine (13%), di-iodotrifluoromethylarsine (4%), b. p. 100°/48 mm., 137°/190 mm., 183°/760 mm. (slight decomp.), and trifluoroiodomethane (5%).

Tristrifluoromethylarsine failed to form an addition compound with mercuric chloride in ethanol at 100° (1 hr.), nor could compound formation be detected with sulphur.

Reaction of Tristrifluoromethylarsine with Chlorine.—Tristrifluoromethylarsine (10·3 g.) and dry chlorine (2·0 g.) were set aside in a sealed Carius tube (50 ml.) at room temperature for 84 hr.; they gave unchanged tristrifluoromethylarsine (6·4 g., 62%), chlorotrifluoromethane (0·5 g., 4%), and *tristrifluoromethylarsenic dichloride* [4·4 g., 34% based on $As(CF_3)_3$ used] (Found: CF_3, 57·0; Cl, 20·1; As, 21·3%; *M*, 340. $C_3Cl_2F_9As$ requires CF_3, 58·6; Cl, 20·1; As, 21·3%; *M*, 353), b. p. 98·5°, n_D^{19} 1·386. Chlorotrifluoromethane was not liberated during the distillation. Analysis for CF_3 was effected by reaction with an excess of 20% sodium hydroxide solution and measurement of the fluoroform evolved. The low molecular weight is caused by partial decomposition of the compound on the mercury of the manometers.

The interaction of tristrifluoromethylarsine (7·6 g.) and chlorine [1·15 g., 61% of the amount for chlorination to $(CF_3)_2AsCl$], in the vapour phase in a 5-l. bulb, followed a different course. After 1·5 hr. fractionation gave chlorotrifluoromethane (1·70 g., 50% based on chlorine), arsenic trichloride (0·18 g.), a mixture (6·39 g.; *M*, 265) of tristrifluoromethylarsine and chlorotrifluoromethylarsines, but no tristrifluoromethylarsenic dichloride.

Tristrifluoromethylarsine (2·8 g.) and chlorine (0·70 g.) in a sealed tube during a month at room temperature gave no tristrifluoromethylarsenic dichloride, but *bistrifluoromethylarsenic trichloride* (*ca.* 30%) (Found: CF_3, 42·1; Cl, 33·2; As, 20·6. $C_2Cl_3F_6As$ requires CF_3, 43·2; Cl, 33·3; As, 23·5%), b. p. 93—95°/722 mm., n_D^{20} 1·423, tristrifluoromethylarsine (1·0 g., 35%), and chlorotrifluoromethane (0·7 g., 22%).

Tristrifluoromethylarsine (14·3 g.) and chlorine (12 g.) at 125° (24 hr.) gave chlorotrifluoromethane and arsenic trichloride in theoretical yield.

When tristrifluoromethylarsenic dichloride was shaken with mercury, tristrifluoromethylarsine (Found: *M*, 280. Calc. for C_3F_9As: *M*, 282) and mercuric chloride were formed. Thermal decomposition of tristrifluoromethylarsenic dichloride (2·0 g.) during 20 hr. at 125° yielded *chlorobistrifluoromethylarsine* (Found: CF_3, 55·7; Cl, 14·3; As, 30·0%; *M*, 249. C_2ClF_6As requires CF_3, 55·5; Cl, 14·3; As, 30·2%; *M*, 248), b. p. 46°, n_D^{19} 1·351, and *dichlorotrifluoromethylarsine* (combined yield *ca.* 38%) (Found: CF_3, 33·0; Cl, 32·2; As, 34·8%; *M*, 215. CCl_2F_3As requires CF_3, 32·1; Cl, 33·0; As, 34·9%; *M*, 215), b. p. 71°, n_D^{20} 1·431, chlorotrifluoromethane (0·2 g., 11%), tristrifluoromethylarsine (*ca.* 10%), and unchanged tristrifluoromethylarsenic dichloride (0·6 g., 31%), b. p. 98°. A small amount of arsenic trichloride was observed. The chlorotrifluoromethylarsines were identical with those obtained from the interaction of the corresponding iodo-compounds and silver chloride (Walaschewski, *loc. cit.*).

Reaction of Tristrifluoromethylarsine with Bromine.—In a typical experiment, tristrifluoromethylarsine (3·4 g.) and bromine [1·80 g., 93% of that required to give $(CF_3)_2AsBr$] in a sealed tube deposited arsenic tribromide (1·2 g., 33%) at −5° and liberated bromotrifluoromethane (1·73 g., 50% based on bromine) (*M*, 152. Calc. for $CBrF_3$: *M*, 149). The residual pale yellow liquid, distilled under atmospheric pressure, gave tristrifluoromethylarsine (1·24 g., 38%), *bromobistrifluoromethylarsine* (0·60 g., 17%) (Found: CF_3, 47·6; Br, 27·3; As, 25·6%; *M*, 280. C_2BrF_6As requires CF_3, 47·1; Br, 27·3; As, 25·6%; *M*, 293), b. p. 59·5°/745 mm., n_D^{20} 1·398, and *dibromotrifluoromethylarsine* (0·40 g., 12%) (Found: CF_3, 22·7; Br, 52·1; As, 24·8. CBr_2F_3As requires CF_3, 22·7; Br, 52·6; As, 24·7%), b. p. 118°/745 mm., n_D^{20} 1·528. Deposition of arsenic tribromide with evolution of bromotrifluoromethane took place even when the reactants were cooled to −22° after initiation of the reaction at −10°, and no indication was obtained of the intermediate formation of tristrifluoromethylarsenic dibromide.

In another experiment in which sufficient bromine was used to give a theoretical conversion into CF_3AsBr_2, excess of bromine was apparent after 3 days at 20°, and reacted further only on distillation of the products, which were similar to those described above.

Reaction of Tristrifluoromethylarsine with Iodine.—The arsine (2·8 g.) dissolved only a small amount of the 2·5 g. of iodine sealed with it, and assumed a reddish colour which, when the supernatant liquid was removed and set aside, slowly disappeared. After the recombined mixture had been heated at 100° for 48 hr., the products were arsenic tri-iodide, iodobistrifluoromethylarsine (*ca.* 8%), di-iodotrifluoromethylarsine (*ca.* 5%), and trifluoroiodomethane (80%). At temperatures above this optimum, increased amounts of arsenic tri-iodide and trifluoroiodomethane were formed.

Tristrifluoromethylarsine (10·5 g.) with arsenic tri-iodide (12·0 g.) at 230—240° (48 hr.) gave trifluoroiodomethane (1·9 g.), iodobistrifluoromethylarsine (3·8 g.), di-iodotrifluoromethylarsine (0·4 g.) and unchanged tristrifluoromethylarsine (6·6 g.) (see Walaschewski, *loc. cit.*).

Reaction of Tristrifluoromethylarsine with Fluorine.—A stream of pure, dry nitrogen was passed through tristrifluoromethylarsine (3·3 g.) in a trap at 10° to carry it during 3·5 hr. over a bed of cobalt trifluoride (20 g.) at 100° in a horizontal copper reaction vessel (9 cm. long, 2 cm. in diameter). The volatile products were fractionated, to give carbon tetrafluoride (1·51 g., 49%), arsenic trifluoride (0·2 g., 13%) (*M*, 137. Calc. for AsF_3: *M*, 132), and a fraction (1·0 g.) (*M*, 266—275) which condensed in a trap cooled to −96°. Examination of the infra-red spectrum of this material showed it to have bands characteristic of *fluorobistrifluoromethylarsine*, independently prepared from iodobistrifluoromethylarsine and silver fluoride at 20° for 3 days (Found: CF_3, 58·9; F^-, 8·1; As, 33·0%; *M*, 228. C_2F_7As requires CF_3, 59·5; F^-, 8·2; As, 32·3%; *M*, 232), b. p. 25°, analysed by decomposition with 10% aqueous sodium hydroxide and measurement of the fluoroform and fluoride. Traces of difluorotrifluoromethylarsine may have been present, but no quinquevalent compounds of arsenic were isolated; *tristrifluoromethylarsenic difluoride* was prepared as a reference compound for this purpose by the interaction of tristrifluoromethyl arsenic dichloride (2·1 g.) and silver fluoride (3 g.) at 20° for 6 days (quantitative yield; 52% conversion) (Found: CF_3, 63·6; F, 11·4; As, 25·0. $C_3F_{11}As$ requires CF_3, 64·7; F, 11·9; As, 23·4%), b. p. 57—58°.

The passage of tristrifluoromethylarsine over cobalt trifluoride at 160° gave almost complete conversion into carbon tetrafluoride and arsenic trifluoride.

The reaction of liquid tristrifluoromethylarsine with elementary fluorine diluted with nitrogen was examined at various temperatures: at −100° and −85° there was little reaction, whilst at −66°, −48°, and −28° carbon tetrafluoride and arsenic trifluoride were formed in increasing amounts. Tristrifluoromethylarsenic difluoride was not isolated.

Bistrifluoromethylarsine.—Iodobistrifluoromethylarsine (2·5 g.) was distilled *in vacuo* into a flask equipped with stirrer and reflux condenser leading to traps cooled in liquid air, and to the frozen arsine was added a solution of lithium aluminium hydride (0·20 g.) in di-*n*-butyl ether (4 ml.). There was a steady gas evolution as the temperature was slowly raised to 10° and the volatile products were swept from the apparatus by a stream of nitrogen. Towards the end of the reaction the temperature was raised to 60° for 10 min. This did not complete the reaction since it was noted in subsequent experiments that a slow evolution of the arsine continued for several days. The product was freed from traces of dibutyl ether and iodobistrifluoromethyl arsine and shown to be *bistrifluoromethylarsine* (0·26 g., 16%) [Found: F, 52·2 (38·1% as CHF_3, 14·1% as F^-); As, 34·9%; *M*, 215. C_2HF_6As requires F, 53·2; As, 35·0%; *M*, 214]. For the analysis, decomposition with 10% aqueous sodium hydroxide gave fluoroform, which was collected and measured, and fluoride and arsenite (see later). The following vapour pressures were recorded: −66·2°, 6·7 mm.; −47·7°, 28·5 mm.; −24·5°, 107·8 mm.; 0°, 349 mm., whence the extrapolated b. p. is 19°. It should be noted that mixing the reactants at room temperature causes a violent gas evolution with loss of product. There is no reaction in the absence of a solvent, which must be chosen to enable the products to be separated easily; tristrifluoromethylarsine shows no reaction with ethereal lithium aluminium hydride at 30—80°.

A better method for the preparation of bistrifluoromethylarsine is as follows: To a 100-ml. flask containing zinc (10 g.) coated with copper, water (10 ml.), and 5N-hydrochloric acid (4 ml.), iodobistrifluoromethylarsine (3·80 g.) was added during 30 min. with vigorous shaking to emulsify the iodo-compound. During 1 hr. further quantities of concentrated acid (10 ml. total) were added, and after flushing with nitrogen for 1 hr. the products which had condensed in traps attached to the reaction flask were fractionated *in vacuo*, to give bistrifluoromethylarsine (1·03 g., 43%) (Found: *M*, 213) and tetrakistrifluoromethyldiarsine (0·87 g., 37%) (Found: *M*, 412. Calc. for $C_4F_{12}As_2$: *M*, 426) (see Part V).

Thermal decomposition of bistrifluoromethylarsine (0·125 g.) in a sealed tube at 220—240° for 40 hr. gave arsenic (as a mirror), fluoroform [0·030 g., 37% based on $(CF_3)_2AsH$] (*M*, 69),

tristrifluoromethylarsine (0·043 g., 39%) (Found: *M*, 278. Calc. for C_3F_9As: *M*, 282), and a mixture of the last compound and bistrifluoromethylarsine (0·015 g.; *M*, 230).

Bistrifluoromethylarsine slowly decomposes at room temperature, and the decomposition is apparently accelerated by traces of impurities in the vacuum system (*e.g.*, mercuric iodide) which was therefore cleaned carefully before use.

Trifluoromethylarsine.—A mixture of di-iodotrifluoromethylarsine (1·52 g.) and lithium aluminium hydride (0·16 g.) in di-*n*-butyl ether (4 ml.), initially frozen in liquid air, was slowly warmed to 15° to give a steady gas evolution. Fractionation of the product *in vacuo* gave *trifluoromethylarsine* (0·24 g., 49%) (Found: F, 37·4%; *M*, 144. CH_2F_3As requires F, 39·1%; *M*, 146), b. p. −12·5°/753 mm., analysed by sodium fusion.

By the alternative procedure, di-iodotrifluoromethylarsine (3·5 g.) was added in 3 portions at 5-min. intervals to zinc (10 g.) coated with copper, water (10 ml.), and 5*N*-hydrochloric acid (25 ml.) with vigorous shaking. Concentrated hydrochloric acid (13 ml.) was then added portionwise during 1 hr., after which the apparatus was flushed with nitrogen for 1 hr. The volatile products were transferred to a vacuum-system and fractionated, to give trifluoromethylarsine (1·26 g., 98%) (Found: F, 39·6%; *M*, 146. Calc. for CH_2F_3As: F, 39·1%; *M*, 146), b. p. −11·6°/781 mm. The reaction of the compound with aqueous sodium hydroxide is described below.

No change was apparent when trifluoromethylarsine (0·329 g.) was heated at 220° for 12 hr., but on further heating at 330° for 40 hr. a grey mirror was produced and hydrogen was liberated. The condensable gas was fluoroform (0·154 g., 98%) (Found: *M*, 69. Calc. for CHF_3: *M*, 70).

Photochemical and Thermal Reactions of Tristrifluoromethylarsine.—(1) *Thermal hydrogenation.* Tristrifluoromethylarsine (1·15 g.), sealed in a Pyrex tube (50 ml.) with hydrogen (630 mm. pressure) and heated to 220—240° for 93 hr., gave arsenic as a grey powder, fluoroform (0·014 g., 2%) identified by its infra-red spectrum, tristrifluoromethylarsine (1·02 g., 89%) (*M*, 283), and an impure fraction of tristrifluoromethylarsine, shown by infra-red spectroscopy to contain no trifluoromethyl- or bistrifluoromethyl-arsine.

(2) *Photochemical hydrogenation.* Tristrifluoromethylarsine (0·639 g.) and hydrogen (560 mm. pressure) in a 120-ml. silica tube were irradiated for 19 hr. by a Hanovia fluorescent lamp at a distance of 4 cm., to give a mixture of fluoroform and hexafluoroethane (0·032 g.) (*M*, 100) identified by its infra-red spectrum, and tristrifluoromethylarsine (0·568 g., 85%) (*M*, 280), but no trifluoromethyl- or bistrifluoromethyl-arsine.

(3) *Photochemical decomposition.* Tristrifluoromethylarsine (0·738 g.) in a 120-ml. silica tube was exposed to ultra-violet light at a distance of 1 cm. for 16 hr. (temp. *ca.* 50°). A film of arsenic was deposited in the cooler parts of the tube, and as volatile products were isolated hexafluoroethane (0·078 g., 14%) (*M*, 139) and tristrifluoromethylarsine (0·6 g., 80%) (*M*, 283).

Preparation of Arsenic Compounds containing Methyl and Trifluoromethyl Groups.—(1) *The exchange reaction.* (*a*) Tristrifluoromethylarsine (0·65 g.) and methyl iodide (0·28 g.) in a 120-ml. silica tube were irradiated at a distance of 1 cm. for 24 hr., to give a trace of unidentified yellow solid, hexafluoroethane (0·07 g., 15%) (*M*, 136·5), trifluoroiodomethane (0·24 g., 18%) (*M*, 197), and a fraction (0·42 g.) (*M*, 237) shown by infra-red analysis to be a mixture containing tristrifluoromethylarsine. The last compound was removed from the mixture by its preferential hydrolysis with 10% aqueous sodium hydroxide at room temperature for 12 hours, and the residual gas (*M*, 217) was shown by its infra-red spectrum to be mainly methylbistrifluoromethylarsine (*ca.* 30%). A portion (0·20 g.) of the gas was sealed with mercuric chloride (1 g.) for 4 months at 20°. The infra-red spectrum of the volatile material was unchanged, but since arsenic was detected in the solid material, and a separate experiment (see below) showed that pure methylbistrifluoromethylarsine did not yield an addition compound with mercuric chloride, the presence of small amounts of dimethyltrifluoromethylarsine and possibly of trimethylarsine is indicated.

(*b*) Tristrifluoromethylarsine (1·77 g.) and methyl iodide (1·63 g.) form two layers at 15°, and these re-appear on cooling after 44 hr.' heating at 140°. After 24 hr. at 235° the pale yellow liquid products remained in one phase, even at −20°. Distillation gave trifluoroiodomethane (1·37 g., 64% based on methyl iodide, 37% on tristrifluoromethylarsine) (Found: *M*, 196. Calc. for CF_3I: *M*, 196) and fluoroform (0·06 g.) as volatile products; 1 : 1 : 1-trifluoroethane was not detected. The less volatile products were a mixture of methyltrifluoromethyl- and bistrifluoromethyl-iodoarsine, which attacked mercury at room temperature with the formation of mercuric iodide, and a mixture of methylbistrifluoromethylarsine and tristrifluoro-

methylarsine (1·5 g.). This mixture was shaken with 10% aqueous sodium hydroxide (30 ml.) for 3 hr., to give fluoroform and methylbistrifluoromethylarsine, identified by comparison of its infra-red spectrum with that of a known specimen (see below).

Tristrifluoromethylarsine and trifluoroiodomethane failed to yield a quaternary salt at 200° (24 hours).

(2) *Interaction of iodobistrifluoromethylarsine and methylmagnesium iodide.* Methylmagnesium iodide (from methyl iodide, 6·0 g., and excess of magnesium in di-*n*-butyl ether, 40 ml.) was filtered and treated dropwise during 20 min. with iodobistrifluoromethylarsine (4·8 g.). No volatile products were detected at this stage, but addition of 10% sulphuric acid (25 ml.) (addition of water liberated only *ca.* 50% of the arsine), followed by slow distillation through a short column, gave a volatile fraction, b. p. 40—100°, which was dried (P_2O_5) and redistilled through a short column, to give *methylbistrifluoromethylarsine* (2·02 g., 63%) (Found: F, 49·0%; *M*, 218. $C_3H_3F_6As$ requires F, 50·0%; *M*, 228), b. p. 52°. Methylbistrifluoromethylarsine failed to yield an addition compound when sealed with mercuric chloride for 2 days at room temperature.

Hydrolysis of Trifluoromethyl Arsenicals.—(1) The following compounds, when treated with 15—20% aqueous sodium hydroxide at room temperature for 12 hr., liberate their trifluoromethyl groups as fluoroform quantitatively: $(CF_3)_3As$, $(CF_3)_2AsX$, X = Br, Cl, F, I, CN, or SCN; CF_3AsX_2, X = Br, Cl, I; $(CF_3)_3AsX_2$, X = Cl, F; $(CF_3)_2AsCl_3$, $(CF_3)_2As{\cdot}O{\cdot}As(CF_3)_2$ (b. p. 100°, n_D^{20} 1·354; prepared quantitatively from iodobistrifluoromethylarsine and mercuric oxide at room temperature).

(2) *Methylbistrifluoromethylarsine.* When this compound (0·207 g.) was shaken with 20% sodium hydroxide (5 ml.) for 3 days at room temperature, decomposition was incomplete [Found: CF_3 (as CHF_3), 41·5; As, 18·5. Calc. for $C_3H_3F_6As$: CF_3, 60·5; As, 32·9%], and unchanged methylbistrifluoromethylarsine was recovered; a test for fluoride was negative. In a second experiment, methylbistrifluoromethylarsine (0·572 g.) was heated at 100° for 72 hr. with 20% aqueous sodium hydroxide (5 ml.) but decomposition was still incomplete (Found: CF_3, 56·8; As, 30·1%), and unchanged fluoroarsine but no fluoride was detected.

(3) *Tetrakistrifluoromethyldiarsine.* The diarsine was prepared quantitatively from iodobistrifluoromethylarsine and mercury (Part V) and purified by distillation at atmospheric pressure (Found: *M*, 426. Calc. for $C_4F_{12}As_2$: *M*, 426), b. p. 105°/770 mm. When the diarsine (0·700 g.) was heated at 100° for 6 hours with 20% sodium hydroxide solution (5 ml.), the rate of hydrolysis was considerably slower than that of tristrifluoromethylarsine under comparable conditions [Found: F, 53·6 (44·8 as CHF_3, 8·8 as F^-); As, 33·9. Calc. for $C_4F_{12}As_2$: F, 53·3; As, 35·2%]. The ratio of fluoroform to fluoride is thus 83·5 : 16·5. The discrepancy in the arsenic figure is ascribed to the formation of a small amount of a bright yellow precipitate, unidentified, but, from the above analysis, apparently consisting entirely of arsenic (cf. the hydrolysis of the trifluoromethyl- and bistrifluoromethyl-arsine, below).

(4) *Bistrifluoromethylarsine.* The compound (0·117 g.) sealed with 15% aqueous sodium hydroxide (5 ml.) and shaken at 20° for 24 hr. gave fluoroform (0·055 g., 38%) and, by distillation of the aqueous solution, fluoride (14%). The percentage of the total fluorine appearing as fluoride was thus 73%.

In a second experiment, precautions were taken to keep disproportionation of the arsine to a minimum, and it was transferred as rapidly as possible to the hydrolysis tube. The arsine (0·279 g.) and 20% aqueous sodium hydroxide (5 ml.) were heated under the "standard conditions" (100° for 2 days) used for the hydrolysis of tetrakistrifluoromethyldiarsine, to give fluoroform (0·118 g., 34·5% of the hydride), and fluoride (0·052 g., 18·5%). The ratio of CF_3 as fluoroform to CF_3 as fluoride is thus 41·7 : 20·4, *i.e.*, approximately 2 : 1. Titration of the aqueous solution with iodine gave arsenic (0·0914 g., 33%) (Calc. for C_2HF_6As: F, 53·2; As, 35·0%). A small amount of a yellow solid formed during the hydrolysis was discarded.

(5) *Trifluoromethylarsine.* The compound (0·220 g.) was sealed with 20% sodium hydroxide solution (5 ml.) and heated at 100° for 6 hr. under the conditions used for tetrakistrifluoromethyldiarsine. A copious, bright yellow precipitate formed was separated by centrifuging, and the fluoride and arsenic in the alkaline solution were determined (Found: F^-, 22·8; As, as $As^{III} + As^V$, 43·2; as As^{III} 14·7%). The volatile product of hydrolysis was fluoroform (equiv. to F^-, 12·5%). The yellow precipitate was slightly soluble in hot water, readily soluble in warm dilute nitric acid with production of a faint garlic odour; after its oxidation the arsenic was determined as $Mg_2As_2O_7$ (Found: additional As, 7·9%). The total arsenic figure is thus 51·1% and the total fluorine figure is 35·3% (Calc. for CH_2F_3As: F, 39·1; As, 51·8%). The

low fluorine figure is due to the small amount of fluorine (not estimated) in the yellow precipitate. Infra-red examination of the yellow solid showed only a broad band at 9·1 μ.

In a second experiment the arsine (0·257 g.) was sealed with 20% aqueous sodium hydroxide (5 ml.) and immediately inserted into a preheated furnace at 105° where it was left for 15 hr. Fluoroform (0·046 g., 14·5%) was produced (cf. 12·5% above).

(6) *Tristrifluoromethylarsine.* The arsine is stable to water at room temperature. Tristrifluoromethylarsine (0·804 g.) was shaken in a 250-ml. flask with buffer solution (100 ml.; McIlvaine's, 13·05% of 0·1M-citric acid, 86·95% of 0·2M-disodium phosphate; pH 7·2), for 48 hr. at 16—20°, and gave fluoroform (0·006 g., 1%) (*M*, 66) and unchanged tristrifluoromethylarsine (0·785 g., 98%). Under identical conditions the arsine (0·705 g.) and buffer solution (100 ml.; Sørensen's, 80% of a solution of 7·505 g. of glycine and 5·85 g. of sodium chloride in 1 l. of water, and 20% of 0·1M-sodium hydroxide; pH 9·3) gave fluoroform (0·076 g., 15%) (*M*, 70) and unchanged tristrifluoromethylarsine (0·547 g., 78%). The arsenic liberated (as arsenite) was 15%.

When tristrifluoromethylarsine (0·572 g.) was shaken at room temperature for 44 hr. with 85% of the amount of sodium hydroxide (35 ml. of 0·049N) required for removal of only one trifluoromethyl group, the volatile products were fluoroform (0·370 g., 87%) (*M*, 70) and tristrifluoromethylarsine (0·069 g., 12%). The aqueous solution was alkaline.

Attempts to achieve stepwise hydrolysis by use of alcoholic sodium hydroxide solutions of various concentrations and following the reaction by the pressure of fluoroform evolved, were unsuccessful.

The stability of tristrifluoromethylarsine to concentrated sulphuric acid was shown as follows: the arsine (5·50 g.) and acid (2 ml.), heated at 150° for 9 hr., gave fluoroform (0·027 g., 0·5%) (*M*, 68), an unidentified gas (0·074 g.) (*M*, 146), and tristrifluoromethylarsine (5·26 g., 96%). The recovered material was reheated with the acid to 235° for 3 hr., to give a fraction (0·160 g.) (*M*, 73) containing fluoroform, silicon tetrafluoride, and carbonyl fluoride, and unchanged tristrifluoromethylarsine (*ca.* 5 g.).

(7) *Cyanobistrifluoromethylarsine.* The compound (1·73 g.) and water (4 ml.), heated at 72° for 38 hours, then at 104° for 60 hr., gave white crystals of arsenic trioxide and fluoroform (0·96 g., 96%) (*M*, 72), separated from hydrogen cyanide (0·18 g., 92%) (*M*, 28) by treatment with sodium hydroxide solution. Traces of cyanogen may have been present.

(8) *Chloro- and iodo-bistrifluoromethylarsines and dichlorotrifluoromethylarsine.* Chlorobistrifluoromethylarsine and dichlorotrifluoromethylarsine failed to react with water at room temperature. Iodobistrifluoromethylarsine is similarly stable, and during 50 hr. at 100° gave less than 2% of fluoroform. After 14 hr. at 260° the iodo-compound decomposed, with attack on the reaction tube, to give silicon tetrafluoride and fluorosilicic acid. The oxidative hydrolysis of the iodo-compound is described below.

(9) *Di-iodotrifluoromethylarsine.* No volatile products were detected after the iodo-compound (0·70 g.) had been shaken vigorously with water (1·5 ml.) at room temperature for 2 weeks, and removal and analysis of the lower layer showed it to be substantially unchanged. The aqueous layer had pH 1 owing to traces of iodine present in the di-iodotrifluoromethylarsine.

Attempts to Prepare Salts of Bistrifluoromethylarsinous Acid.—Iodobistrifluoromethylarsine (1·1 g.) and silver oxide (1·16 g.; washed with dilute acetic acid) rapidly yielded silver iodide, precipitated from a neutral solution. It proved impossible to separate the silver salt, believed to be $(CF_3)_2As{\cdot}OAg$ from silver iodide. The salt is decomposed by alkali, nitric acid, hydrogen sulphide, or neutral potassium iodide with the evolution of fluoroform. Interaction of iodobistrifluoromethylarsine (2·1 g.) and mercuric oxide (2 g.) in water (3 ml.) gave mercuric iodide and a slow deposition of white needles which were separated by dissolution in an excess of water, filtration, and evaporation of the solution to dryness *in vacuo* at room temperature. The *mercury* salt [Found: F, 30·1 (29·0% as CHF_3, 1·1% as F^-); As, 22·8; Hg, 29·9. $C_4F_{12}O_2As_2Hg$ requires F, 34·6; As, 22·7; Hg, 30·5%] does not melt below 310°.

Bistrifluoromethylarsinic Acid (*Hexafluorocacodylic Acid*).—Iodobistrifluoromethylarsine (5·04 g.) was sealed in a Pyrex tube with unstabilised hydrogen peroxide (100-vol.; 3 ml.). Warming to room temperature caused exothermic liberation of iodine which was substantially complete in 15 min. If the reaction was not interrupted at this stage, fluoroform was slowly liberated (*ca.* 8% after 3 days). The iodine was removed by filtration, and the strongly acid solution was evaporated to dryness over sulphuric acid in an evacuated desiccator (much of the arsinic acid is lost by removal of the water by continued pumping). Large translucent trigonal rhombs were obtained which, after 2 hr. in the desiccator, lost water and changed to a white powder (3·11 g., 86%). The solid was recrystallised from hot chloroform to remove

traces of arsenic oxides and gave *bistrifluoromethylarsinic acid* (Found : CF_3, 56·7; As, 30·8. $C_2HF_6O_2As$ requires CF_3, 56·1; As, 30·5%), analysed by treatment with 20% aqueous sodium hydroxide at 100° for 6 hr.; fluoride was not formed.

Bistrifluoromethylarsinic acid is readily soluble in water, less soluble in dioxan and hot chloroform. It does not melt, but sublimes with partial decomposition at 150°/10^{-3} mm. to give needles (Found : CF_3, 56·9; As, 31·9%) of the free acid, possibly contaminated with anhydride (Calc. for $C_4F_{12}O_3As_2$: CF_3, 58·2; As, 31·7%). The brown residue from the sublimation liberates fluoroform on treatment with aqueous alkali.

When bistrifluoromethylarsinic acid (0·077 g.) was treated with an excess of 50% sulphuric acid at 135—145°, no hydrolysis to fluoride ion was detected on titration of the distillate with thorium nitrate.

Conductivity. The conductivites at 25° of bistrifluoromethylarsinic acid and dimethylarsinic acid (cacodylic acid) are :

Dilution (l. mole^{-1})	32	64	128
Molecular conductivity :			
$(CF_3)_2AsO_2H$	314	348	359
$(CH_3)_2AsO_2H$	1·37	1·96	2·76

Titration. A solution of 0·769 g. of the acid in water (100 ml.) (*i.e.*, M/32) had pH 1·67 (cf. M/32-hydrochloric acid, pH 1·50). Titration of 5 ml. against 0·1N-sodium hydroxide can be carried out accurately only below pH 7, since fluoroform is lost in alkaline solution. The solution was stirred by a fine stream of nitrogen and the pH was measured by a Cambridge Instrument Co. pH meter. The first point of inflection (pH 3·7) is at 1·60 ml. of alkali [$(CF_3)_2As{\cdot}ONa$ or $(CF_3)_2As(OH)_2(ONa)$ requires 1·56 ml.]. *Rapid* titration with base gives a second point of inflection at *ca.* pH 9, corresponding approximately to the equivalent for $(CF_3)_2As(OH)(ONa)_2$ (3·1 ml.). *Slow* titration of the acid with base gives completely reproducible results up to pH 7, but the decomposition of the acid at pH >7 is shown by the solution obtained from the acid (0·0217 g.) dissolved in water (10 ml.) and treated with 0·1N-sodium hydroxide (1·65 ml.); the pH after 0, 3, 6, 37, and 267 min. was 8·33, 8·23, 8·12, 7·63, and 6·98 respectively.

Silver salt. A solution of the acid in water was treated with a 50% excess of silver oxide, and the mixture was heated to 60° until pH 7 was attained (10 min.). The excess of oxide was removed by centrifuging and the aqueous solution was evaporated over sulphuric acid in an evacuated desiccator, to give glittering trigonal crystals which were recrystallised from acetone to give the *silver* salt (Found : CF_3, 38·6; As, 20·5; Ag, 29·8. $C_2F_6O_2AsAg$ requires CF_3, 39·1; As, 21·1; Ag, 30·6%). The salt is very soluble in water; in hot alcohol it becomes brown. The salt does not melt, but becomes brown at 100° and at 250° liberates arsenic trioxide. The trifluoromethyl groups were liberated quantitatively as fluoroform on treatment with aqueous sodium hydroxide.

Ultra-violet and Infra-red Spectra.—A Beckman DU spectrophotometer and a Perkin–Elmer Model 21 Double-beam instrument with rock-salt optics were used. Quartz cells of 10- or 4-cm. length, and 5- or 10-cm. cells with rock-salt end plates were used where appropriate. Nujol and hexachlorobutadiene mulls were used for solid compounds.

Cyanobistrifluoromethylarsine, b. p. 89·5°, n_D^{20} 1·359, and thiocyanatobistrifluoromethylarsine, b. p. 117°, n_D^{20} 1·445, were prepared from iodobistrifluoromethylarsine and the appropriate silver salt. The infra-red spectra show C⋮N absorption at 4·57 μ, and SCN absorption at 5·0 μ. No pressure was recorded for tristrifluoromethylarsenic dichloride, since the compound attacks mercury. The spectrum of silver bistrifluoromethylarsinate (C.S. no. 35*) contains weak bands at *ca.* 3 and 6·17 μ, indicating the presence of water as impurity, possibly as a hydrate.

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* Cf. footnote, p. 1556.

317. *Organometallic and Organometalloidal Fluorine Compounds. Part VII.* Trifluoromethyl Compounds of Phosphorus.†*

By F. W. Bennett, H. J. Emeléus, and R. N. Haszeldine.

The interaction of phosphorus and trifluoroiodomethane at 200—220° yields tristrifluoromethylphosphine, $P(CF_3)_3$, iodobistrifluoromethylphosphine, $P(CF_3)_2I$, di-iodotrifluoromethylphosphine, $P(CF_3)I_2$, and phosphorus iodides. The trifluoromethyl compounds are quantitatively hydrolysed to fluoroform by dilute sodium hydroxide solution. Their conversion into $(CF_3)_3PCl_2$, $(CF_3)_2PCl$, $(CF_3)_2P{\cdot}CN$, $CF_3{\cdot}PCl_2$, and $(CF_3)_2P{\cdot}P(CF_3)_2$ is described. The iodo-compounds disproportionate when heated. Comparisons are made with the methyl analogues, and ultra-violet and infra-red spectra are presented and discussed.

The methods commonly used for the preparation of alkyl derivatives of phosphorus cannot readily be applied to the preparation of the corresponding perfluoroalkyl derivatives, but the direct interaction of white phosphorus and a perfluoroalkyl iodide such as trifluoroiodomethane has proved successful. This reaction, which is believed to involve radical intermediates, can be carried out in sealed Pyrex tubes or in stainless-steel autoclaves, and, in the optimum temperature range of 200—220°, yields tristrifluoromethylphosphine, iodobistrifluoromethylphosphine, di-iodotrifluoromethylphosphine, tetraiododiphosphine, and phosphorus tri-iodide. At the higher temperature over 80% of the product other than trifluoroiodomethane consists of tristrifluoromethylphosphine; below 200° the reaction is slow, but produces a higher percentage yield of the iodo-compounds which, because of the reactivity of the iodine atoms, are of greater chemical interest. Somewhat increased yields of the iodotrifluoromethylphosphines may be obtained by use of red phosphorus instead of white, but the most convenient method is to heat white phosphorus and trifluoroiodomethane at the optimum temperature, remove the iodo-compound by a rough fractionation *in vacuo*, and recycle the tristrifluoromethylphosphine and unchanged trifluoroiodomethane. The use of a mixture of phosphorus and phosphorus tri-iodide also increases the proportion of iodobistrifluoromethylphosphine in the complex equilibria:

$$(CF_3)_3P \rightleftharpoons (CF_3)_2PI \rightleftharpoons CF_3{\cdot}PI_2 \rightleftharpoons CF_3I + P$$

Hexafluoroethane is not formed, nor are quaternary phosphonium compounds isolated (cf. ethyl iodide and phosphorus: Carius, *Annalen*, 1866, **137**, 117; Crafts and Silva, *J.*, 1871, 629; Masson and Kirkland, *J.*, 1889, 135; methyl iodide: Auger, *Compt. rend.*, 1904, **139**, 639, 671). The excess of white phosphorus used in the reaction is converted into red phosphorus, a change known to be catalysed by iodine. Reaction of excess of phosphorus with trifluoroiodomethane above 250° gives phosphorus tri- and pentafluoride and hexafluoroethane as major products.

The iodotrifluoromethylphosphines disproportionate when heated, and the equilibria indicated above can also be set up by heating tristrifluoromethylphosphine with iodine:

$$2(CF_3)_2PI \rightleftharpoons (CF_3)_3P + CF_3{\cdot}PI_2$$
$$2CF_3{\cdot}PI_2 \rightleftharpoons (CF_3)_2PI + PI_3$$
$$(CF_3)_3P + I_2 \rightleftharpoons (CF_3)_2PI + CF_3I$$

The arsenic analogues show similar behaviour (Part V, *J.*, 1952, 2552).

Tristrifluoromethylphosphine is a colourless, spontaneously inflammable liquid which boils (17°) some 20° below its methyl analogue (b. p. 37·8°; Rosenbaum and Sandberg, *J. Amer. Chem. Soc.*, 1940, **62**, 1622) [cf. $As(CF_3)_3$, b. p. 33·3°, and $AsMe_3$, b. p. 49·5°, Part VI, *loc. cit.*]. The chlorine analogue of tristrifluoromethylphosphine is unknown, but Hoffman (*J. Amer. Chem. Soc.*, 1930, **52**, 2995) reports b. p. 100°/7 mm. for $P(CH_2Cl)_3$. Compounds comparable in molecular weight to tristrifluoromethylphosphine are triphenyl-

* Part VI, preceding paper. † Preliminary publications: *Nature*, 1950, **166**, 225; New York City Meeting, Amer. Chem. Soc., Sept., 1951.

phosphine (b. p. >360°; Michaelis, *Annalen*, 1885, **229**, 295) and tributylphosphine (b. p. 150°/50 mm.; Davies and Jones, *J.*, 1929, 33).

Tristrifluoromethylphosphine is markedly different from trialkylphosphines by virtue of its strongly electronegative trifluoromethyl groups. The unsubstituted alkylphosphines (*e.g.*, PMe_3) are characterised by compound formation with carbon disulphide, sulphur, silver iodide, and other metallic salts, but introduction of fluorine into the molecule prevents, or at least appreciably inhibits, such compound formation. No reaction could be detected between tristrifluoromethylphosphine and sulphur or carbon disulphide at temperatures up to 200°. Triarylphosphines similarly do not react with carbon disulphide although they react smoothly with sulphur. The trifluoromethyl group acts like a pseudo-halogen in this connection, since phosphorus trichloride reacts with sulphur only at 140°, and no carbon disulphide addition compound has been reported; and phosphorus trifluoride fails to react with sulphur even at 440° (Moissan, " Le Fluor et ses Composés," Steinheil, Paris, 1900, p. 160).

Chlorine reacts violently with trialkylphosphines with attack on the alkyl groups, to give a mixture of chloroalkyl phosphines, but tristrifluoromethylphosphine at −40° smoothly gives tristrifluoromethylphosphorus dichloride in almost quantitative yield. The methyl analogue of the quinquevalent phosphorus compound (Me_3PCl_2) has not been described, although the phenyl analogue has been obtained by a reaction at −80° (Jensen, *Z. anorg. Chem.*, 1943, **250**, 257). Tristrifluoromethylphosphorus dichloride can be distilled without decomposition at 370 mm., but explodes violently near the b. p. at 760 mm. (*ca.* 94°).

Tristrifluoromethylphosphine and iodine react only at >100°, and no intermediate addition compound, $(CF_3)_3PI_2$, has been detected; iodotrifluoromethylphosphines, trifluoroiodomethane, and phosphorus tri-iodide are formed.

Iodobistrifluoromethylphosphine and di-iodotrifluoromethyl phosphine are liquids (b. p. 73° and 69°/29 mm. respectively), which liberate iodine on exposure to light. The former is rapidly oxidised in air. Like tristrifluoromethylphosphine they are rapidly and quantitatively hydrolysed by dilute aqueous alkali, and the trifluoromethyl groups are liberated as fluoroform; the arsenic compounds behave similarly (Part V, *loc. cit.*). Unlike the iodo-trifluoromethyl arsenicals and tristrifluoromethylphosphine, the iodotrifluoromethylphosphines are rapidly decomposed by water at room temperature. One molecular proportion of fluoroform is liberated from iodobistrifluoromethylphosphine, whereas no fluoroform is obtained from the di-iodo-compound. In the latter case, evaporation of the hydrolysis product *in vacuo* yields a white, hygroscopic, crystalline, strong, dibasic acid, which shows reducing properties. The constitution of this acid, which on oxidation yields a second strong, dibasic acid, $CF_3 \cdot PO(OH)_2$, is being studied in greater detail.

The iodine atoms in iodobistrifluoromethyl- and di-iodotrifluoromethyl-phosphine are reactive and may be replaced by other halogens or pseudo-halogens. Thus, with silver chloride almost quantitative yields of chlorobistrifluoromethylphosphine and dichlorotrifluoromethylphosphine are obtained, and with silver cyanide the mono-iodo-compound yields cyanobistrifluoromethylphosphine:

$$(CF_3)_2PI \xrightarrow{AgX} (CF_3)_2PX; \quad CF_3 \cdot PI_2 \xrightarrow{AgX} CF_3 \cdot PX_2$$

These volatile compounds are readily hydrolysed by aqueous alkali with quantitative evolution of fluoroform, but unlike the parent iodo-compounds do not react with mercury at room temperature.

Iodobistrifluoromethylphosphine reacts with mercury at room temperature to give tetrakistrifluoromethyldiphosphine, a stable, colourless liquid, b. p. 84°:

$$2(CF_3)_2PI + Hg \longrightarrow (CF_3)_2P \cdot P(CF_3)_2 + HgI_2$$

Iodobistrifluoromethylarsine reacts similarly with mercury, but whereas cacodyl, the methyl analogue of the arsenic compound, is well known, the preparation of the methyl derivative of diphosphine has not been definitely established. Attachment of the strongly electronegative fluoroalkyl groups to metalloidal atoms M (= P, As, Sb, S, Se) thus stabilises

the M–M bond. The linking of two phosphorus atoms by the reaction described above is novel in phosphorus chemistry, and few compounds containing the P–P bond are known. The existence of tetraphenyldiphosphine (b. p. 400°) seems established (Köhler and Michaelis, *Ber.*, 1877, **10**, 807) but few of its reactions have been reported. Halogen derivatives of diphosphine are known (P_2Cl_4, P_2I_4; Besson and Fournier, *Compt. rend.*, 1910, **150**, 102; Gay-Lussac, *Ann. Chim. Phys.*, 1814, **91**, 9; Doughty, *J. Amer. Chem. Soc.*, 1905, **27**, 1444; Germann and Traxler, *ibid.*, 1927, **49**, 307), and also diphosphine itself (Gattermann and Haussknecht, *Ber.*, 1890, **23**, 1174), and it would be expected that P_2F_4 should also exist.

The constitution of tetrakistrifluoromethyldiphosphine has been established by its reaction with iodine at 280°, four mols. of trifluoroiodomethane being obtained; bromine similarly yields four mols. of bromotrifluoromethane. Treatment of tetrakistrifluoromethyldiphosphine with aqueous alkali liberates only part of the fluorine as fluoroform, the remainder forming fluoride and bistrifluoromethylphosphinous acid. It is believed that hydrolysis occurs by attack on the P–P bond :

$$(CF_3)_2P{\cdot}P(CF_3)_2 \longrightarrow (CF_3)_2PH + (CF_3)_2P{\cdot}OH$$

and a detailed quantitative study in support of this mechanism will be reported in a later paper.

Tristrifluoromethylphosphine shows only end absorption in the ultra-violet. Step-wise replacement of the trifluoromethyl groups by iodine produces the expected shifts to the red, as shown in Table 1. The figures show that solvent shifts are small. The corresponding data for the arsenic compounds (Part VI, *loc. cit.*), summarised in Table 2 (light petroleum solutions), show that the spectra are very similar but with a bathochromic shift on changing from phosphorus to arsenic. This effect is also shown by comparison of tristrifluoromethyl-phosphine and -arsine (Table 3). The marked chromophoric effect of the P–P bond is shown by the spectrum of tetrakistrifluoromethyldiphosphine ($\lambda_{max.}$ 216 mμ; ε *ca.* 4000) [cf. $(CF_3)_2As{\cdot}As(CF_3)_2$, $\lambda_{max.}$ 223; ε 3000; Part VI].

TABLE 1.

	Solvent	$\lambda_{max.}$	$\varepsilon_{max.}$	$\lambda_{min.}$	$\varepsilon_{min.}$	$\lambda_{infl.}$	ε
$(CF_3)_2PI$	Light petroleum	282	900	246	280	—	—
	Ether	279	1,000	248	500	—	—
	Vapour	278	1,200	241	400	—	—
CF_3PI_2	Ether	266	5,900	246	4000	320	2600
	Light petroleum	267	3,800	244	2300	320	1400
PI_3	Ether	360	8,800	324	5840	—	—
		291	14,500	248	2000	—	—

TABLE 2.

	$\lambda_{max.}$	$\varepsilon_{max.}$		$\lambda_{max.}$	$\varepsilon_{max.}$
$(CF_3)_2AsI$	290	1200	AsI_3	378	1,600
CF_3AsI_2	271	4200		280	5,600
	229	6500		225	12,000
	$\lambda_{infl.}$ 325 (ε, 1700)				

TABLE 3.

$(CF_3)_3P$	λ	250	240	230	220
	ε	—	—	2·1	11·7
$(CF_3)_3As$	ε	1·89	6·75	12·6	18·7

The infra-red spectra of certain trifluoromethylphosphorus derivatives are recorded in the Experimental, and are useful for identifications. The carbon–fluorine stretching vibrations lie in the 8—9-μ region, showing two main maxima for compounds $CF_3{\cdot}PX_2$ (X = Cl, I); compounds $(CF_3)_2PX$ (X = I, CN) show three main maxima, and $(CF_3)_3P$ has four maxima in this region. Like the arsenic compounds (Part VI), the phosphorus compounds show a strong band at *ca.* 13·3 μ [$CF_3{\cdot}PI_2$ 13·5; $(CF_3)_2PI$ 13·4; $(CF_3)_2P{\cdot}P(CF_3)_2$ 13·37; $(CF_3)_2P{\cdot}CN$, $(CF_3)_2PCl$, $CF_3{\cdot}PCl_2$ 13·3; $(CF_3)_3P$ 13·25 μ], which is probably a CF_3 deformation frequency rather than a C–P stretching vibration. Daasch and Smith (*Ind. Eng.*

Chem., 1951, **23**, 853) have attributed bands in this region to C–P stretching vibrations in certain compounds, and their data suggest that, if correctly assigned, the vibration moves to shorter wave-length with increase in negativity of the groups attached to phosphorus [PMe_3, 14·1, 15·3; $Et{\cdot}PCl_2$, 13·2, 13·8; $CCl_3{\cdot}PO(OEt)_2$, 13·0, 13·5]. Overtones of the C–F vibrations are apparent at *ca.* 4·4 μ, and for cyanobistrifluoromethylphosphine the sharp absorption band at 4·56 μ is the C≡N stretching vibration.

Experimental

General Technique.—The phosphorus compounds were manipulated in absence of air in a vacuum-system where practicable. Reactions were carried out in Pyrex tubes (30—50 ml.), sealed *in vacuo* with careful exclusion of air and moisture, or in stainless-steel autoclaves (100 or 300 ml.); reaction products were transferred *in vacuo*, and purified by fractional condensation or by distillation through a short column in an atmosphere of nitrogen. B. p.s were determined by distillation or by an isoteniscope, and molecular weights by Regnault's method.

Analysis.—Many of the compounds prepared were rapidly and quantitatively hydrolysed to fluoroform and phosphite by treatment with 10% aqueous hydroxide (10 ml.); the reaction is fast, but at least 24 hr. were allowed to ensure its completion. Fluoroform was measured in the vacuum-system, and the aqueous phase was analysed for halogen (when present), or was oxidised with nitric acid, and phosphorus determined as phosphomolybdate. Ionic fluorine was determined by titration with thorium nitrate, and covalent fluorine by sodium fusion followed by steam-distillation of the acidified solution and titration with thorium nitrate.

Note. The use of sodium peroxide instead of sodium for fusion causes violent explosions.

Preparation of Trifluoroiodomethane.—The preparation from silver trifluoroacetate (Haszeldine, *J.*, 1951, 584) was adapted to a large scale: silver trifluoroacetate (1 mole) and powdered iodine (1·6 moles) were mixed in a 4-l. flask, and reaction was initiated by heating a small section of the flask with a free flame. Heating was controlled to give a steady evolution of gas which was passed up a tower down which 10% aqueous sodium hydroxide was running. After drying over phosphoric anhydride the crude trifluoroiodomethane was purified in the vacuum-system (0·9 mole).

The method of *J.*, 1948, 2188 was used in the earlier experiments.

Reaction of Phosphorus with Trifluoroiodomethane.—Commercial stick phosphorus was purified by dipping it into carbon disulphide until the outer oxide layer became detached, and was transferred in a carbon dioxide atmosphere to the reaction vessel and dried *in vacuo*. In a typical early experiment, trifluoroiodomethane (2·94 g.) was sealed *in vacuo* in a Carius tube containing purified phosphorus (3 g.). There was no reaction after 24 hr. at 100°, but after 48 hr. at 220° the tube contained a red solid and a liquid less volatile than trifluoroiodomethane. Fractionation gave unchanged trifluoroiodomethane (30%), *tristrifluoromethylphosphine* (0·7 g., 84%) [Found: C, 14·2; CF_3 (as CHF_3), 86·4; P, 13·5%; *M*, 238. C_3F_9P requires C, 15·1; CF_3, 86·9; P, 13·1%; *M*, 238], *iodobistrifluoromethylphosphine* (0·3 g., 15%), b. p. 72—73°, n_D^{15} 1·403 [Found: C, 8·6; CF_3 (as CHF_3) 46·9; I, 42·5; P, 10·4%; *M*, 297. C_2F_6IP requires C, 8·1; CF_3, 46·9; I, 42·8; P, 10·5%; *M*, 296], and *di-iodotrifluoromethylphosphine* (0·05 g., 1%), b. p. 69°/29 mm., n_D^{20} 1·630 [Found: CF_3 (as CHF_3) 16·6; I, 72·7; P, 8·1. CF_3I_2P requires CF_3, 16·7; I, 71·8; P, 8·8%]. Yields are based on trifluoroiodomethane used, and for the two iodo-compounds are values from bulked products from a number of tubes of the above type. Phosphorus iodides were detected qualitatively in the involatile red solid residue.

Red phosphorus (3 g.), purified by washing with 10% aqueous sodium hydroxide, water, and ethanol and dried *in vacuo*, was similarly heated at 260° for 48 hr. with trifluoroiodomethane (3·8 g.), to give tristrifluoromethylphosphine (0·85 g., 54%) (*M*, 237), iodobistrifluoromethylphosphine (0·71 g., 24%) (*M*, 295), di-iodotrifluoromethylphosphine (0·05 g., 1%), and trifluoroiodomethane (0·226 g., 6%) (*M*, 196).

Results obtained for the reaction of trifluoroiodomethane (50 g.) with white phosphorus (50 g.) in a 300-ml. autoclave are shown in the annexed table (yields based on CF_3I used).

Temp.	$P(CF_3)_3$	$P(CF_3)_2I$	$P(CF_3)I_2$	CF_3I recovered
195°	0·5 g., 25%	2 g., 32%	6 g., 42%	*ca.* 85%
210	1·5 g., 47%	1·5 g., 21%	4 g., 28%	*ca.* 85%
230	7·1 g., 70%	3·7 g., 20%	2·7 g., 6%	50%

Optimum yields of iodo-compounds were obtained by heating trifluoroiodomethane (70 g.) with phosphorus (50 g.) at 195—200° for 48 hr., separating the iodo-compounds in the product by a rough vacuum-fractionation, and recycling the tristrifluoromethylphosphine and unchanged

trifluoroiodomethane without addition of fresh phosphorus to the autoclave until *ca.* 10 g. of the fluoro-iodide remained (3 times). The products were tristrifluoromethylphosphine (3·2 g., 12%), iodobistrifluoromethylphosphine (12 g., 23%), di-iodotrifluoromethylphosphine (48 g., 37%), and trifluoroiodomethane (14·5 g., 21%). Improved yields of the iodo-compounds were also obtained by heating phosphorus (50 g.), iodine (50 g.), and trifluoroiodomethane (60 g.) to 200° for 48 hr., removing the iodo-compounds and recycling three times as above: tristrifluoromethylphosphine (3·14 g., 13%), iodobistrifluoromethylphosphine (8·65 g., 19%), di-iodotrifluoromethylphosphine (19·2 g., 18%), and trifluoroiodomethane (29 g., 49%).

A large excess of phosphorus (*e.g.*, 150 g. instead of 50 g.) favours formation of phosphorus trifluoride and hexafluoroethane.

Properties and Reactions of Tristrifluoromethylphosphine.—The compound is a liquid which solidifies to a glass when cooled in liquid nitrogen. It can be heated in glass to 200° without decomposition, is insoluble in, denser than, and stable to, air-free water at room temperature, and inflames in air. The vapour pressure, determined by standard techniques over the range −25° to 12°, is expressed by the formula $\log_{10} p$ (mm.) = 7·323 − 1289·6/T, whence the b. p. is 17·3° ± 0·1°, the latent heat of vapourisation 5890 cal./mole, and Trouton's constant 20·3.

No compound formation could be detected when tristrifluoromethylphosphine was heated to 180° for 3 days with sulphur; no change was apparent after the phosphine had been heated with carbon disulphide at 120° for 8 hr., and two layers were still present on cooling. Compound formation could not be detected when silver iodide, or a solution of silver iodide in aqueous potassium iodide, was shaken with tristrifluoromethylphosphine at room temperature, and the phosphine was recovered quantitatively. Mercuric iodide also failed to combine with tristrifluoromethyl phosphine at room temperature. The possibility of compound formation with salts of the platinum metals has not been investigated.

Tristrifluoromethylphosphine (0·188 g.) was recovered unchanged after being heated with water (10 ml.) for 16 hr. at 100°. After 12 hr. at 200°, fluoroform (0·077 g.) was isolated and characterised, representing 46% hydrolysis of the phosphine. The compound was more stable to N-hydrochloric acid, since 99% was recovered after 24 hr. at 180°.

Tristrifluoromethylphosphine (0·392 g.) was condensed in a Pyrex tube containing sodium hydroxide (1 g.) and water (15 ml.), to give an immediate reaction at 20°. After 48 hr. the volatile products yielded fluoroform (0·338 g., 98%) (Found: *M*, 70. Calc. for CHF_3: *M*, 70), identified tensimetrically.

No reaction was detected between iodine (1 g.) and tristrifluoromethylphosphine (0·971 g.) after 12 hr. at 100°, but at 180° crystals of phosphorus tri-iodide were deposited and after 24 hr.' fractionation gave trifluoroiodomethane (0·788 g., 34%) (*M*, 196), iodobistrifluoromethylphosphine (0·262 g., 16%) (*M*, 295), di-iodotrifluoromethylphosphine (0·162 g., 4%), and recovered tristrifluoromethylphosphine (0·419 g., 43%) (*M*, 239). A small amount of fluoroform (0·026 g.) was also present, arising from reaction with traces of moisture retained by iodine even when dried over phosphoric oxide *in vacuo* for 7 days.

Tristrifluoromethylphosphine (2·08 g.) reacted with chlorine (0·575 g.) in a sealed tube at −45°. After 4 hr. the tube was cooled to −63°, and the excess of chlorine removed by pumping to leave a white solid, which was distilled at reduced pressure under nitrogen, to give *tristrifluoromethylphosphorus dichloride* (1·50 g., 56%), b. p. 71°/368 mm., m. p. 20·5° [Found: Cl, 22·9 (Volhard); F, 55·2. $C_3Cl_2F_9P$ requires Cl, 23·0; F, 55·3%]. Attempts to distil the compound at 760 mm. brought about explosive decomposition.

Reactions of Iodobistrifluoromethylphosphine.—The compound is a colourless liquid which attacks mercury, fumes in air, has a pungent smell, and is spontaneously inflammable only in an excess of air. It is best stored at low temperature in the dark, since it liberates iodine on exposure to light.

When the compound (0·517 g.) was heated to 205° for 48 hr. in a sealed 40-ml. tube, disproportionation occurred to give tristrifluoromethylphosphine (0·124 g., 45%) (*M*, 235), iodobistrifluoromethylphosphine (0·242 g., 47%) (*M*, 294), di-iodotrifluoromethylphosphine (0·025 g., 2%), and traces of hexafluoroethane (0·02 g., 8%) and trifluoroiodomethane (0·005 g., 2%), together with characteristic red-orange, prismatic crystals of phosphorus tri-iodide.

Alkaline hydrolysis of iodobistrifluoromethylphosphine (0·188 g.) with 10% aqueous sodium hydroxide (15 ml.) at 20° for 24 hr. gave fluoroform (0·0885 g., 99%) (*M*, 70), and the hydrolysate yielded silver iodide (0·146 g., 98%).

The iodo-compound (0·182 g.) formed a lower layer when sealed with distilled water (10 ml.), but rapidly dissolved, with liberation of gas from the aqueous phase. After 5 days at 20°, the

only volatile product was fluoroform (0·0427 g., 50%). Further experiments gave values of 50 ± 2%. The iodine had been liberated quantitatively as iodide (Found: I, 42·5. Calc. for C_2IF_6P: I, 42·9%).

When the reaction tube was resealed and heated at 100° for 12 hr., a further quantity (0·026 g., 32%) of fluoroform (*M*, 71) was obtained.

The reaction of iodobistrifluoromethylphosphine (0·537 g.) with mineral acid (15 ml. of N-hydrochloric acid) follows a similar course. The immediate reaction soon subsided and after 4 days' fractionation gave fluoroform (0·120 g., 47%) (*M*, 71); by resealing, and heating at 100° for 16 hr., a further quantity of fluoroform (0·125 g., 49%) (*M*, 70) was obtained.

Iodobistrifluoromethylphosphine (0·669 g.), sealed with silver cyanide (0·521 g.) at 20° for 24 hr., gave silver iodide (0·541 g.) and *cyanobistrifluoromethylphosphine* (0·411 g., 95%), b. p. 48°, n_D^{20} 1·3248 [Found: CF_3 (as CHF_3), 70·0; CN, 13·3%; *M*, 195. C_3NF_6P requires CF_3, 70·7; CN, 13·3%; *M*, 195], as a colourless liquid with a spontaneously inflammable vapour.

The iodo-phosphine (0·925 g.) was similarly treated with silver chloride (1·184 g.), to give *chlorobistrifluoromethylphosphine* (0·622 g., 97%), b. p. 21° (Found: CF_3, 67·2; Cl, 17·1%; *M*, 204·5. C_2ClF_6P requires CF_3, 67·3; Cl, 17·3%; *M*, 204·5), as a spontaneously inflammable liquid which does not attack mercury. Treatment of chlorobistrifluoromethylphosphine (0·160 g.) with 10% aqueous sodium hydroxide (10 ml.) gave fluoroform (0·109 g., 100%).

Tetrakistrifluoromethyldiphosphine.—Excess of redistilled mercury (6 ml.) was sealed with iodobistrifluoromethylphosphine (7·11 g.) and shaken vigorously for 2 days, to give mercury iodides and *tetrakistrifluoromethyldiphosphine* (3·34 g., 82%), b. p. 83—84° (Found: C, 13·8; F, 65·5%; *M*, 338. $C_4F_{12}P_2$ requires C, 14·2; F, 67·4%; *M*, 338). Analysis of this compound proved difficult, and no method was found for determining phosphorus directly, since sodium fusion gives some phosphide and attempts to oxidise with sodium peroxide gave explosions; alkaline hydrolysis does not liberate all the fluoroform quantitatively. Unchanged iodo-compound cannot be separated easily from tetrakistrifluoromethyldiphosphine, and it is preferred to bring about complete reaction by vigorous shaking, without which the reaction is incomplete after 3 weeks. The product is a colourless liquid, insoluble in and denser than water, with which it does not react at room temperature. The constitution of this inflammable compound was established by reaction with iodine: the diphosphine (0·340 g.) was sealed with an excess of iodine (7 g.) and heated at 280° for 48 hr., to give trifluoroiodomethane (0·751 g., 95%). A similar reaction with bromine gave bromotrifluoromethane (0·342 g., 94%) (*M*, 147), and analysis of the phosphorus bromides obtained gave P, 17·9% (Calc. for $C_4F_{12}P_2$: P, 18·3%). Tetrakistrifluoromethyldiphosphine was recovered unchanged after 24 hr. heating at 210°.

Reactions of Di-iodotrifluoromethylphosphine.—The compound is a yellow, oily liquid which fumes in air, readily attacks mercury, and liberates iodine. It was purified before use by distillation at reduced pressure from red phosphorus: it had b. p. 133°/413 mm., 103°/132 mm., 73°/37 mm., 69°/29 mm.; it decomposes when heated at 760 mm.

Di-iodotrifluoromethylphosphine (0·385 g.), treated with 10% aqueous sodium hydroxide (10 ml.) at 20° for 48 hr., gave fluoroform (99·5%) (*M*, 70), sodium phosphite, and sodium iodide (100%). The di-iodo-compound reacts readily with water without liberation of fluoroform, to give, on evaporation of the aqueous solution *in vacuo*, a white *substance* of empirical formula $CF_3{\cdot}P(OH)_2{\cdot}H_2O$ [Found: F, 37·2%; *M* (by titration), 152. $CH_4O_3PF_3$ requires F, 37·5%; *M*, 152].

The di-iodo-compound (2·483 g.), heated at 240° for 48 hr., gave trifluoroiodomethane (0·177 g., 13%) (*M*, 195), tristrifluoromethylphosphine (0·130 g., 23%) (*M*, 235), iodobistrifluoromethylphosphine (0·424 g., 41%) (*M*, 292), unchanged di-iodotrifluoromethylphosphine (0·323 g., 13%), and phosphorus tri-iodide.

Interaction of di-iodotrifluoromethylphosphine (0·959 g.) and silver chloride (1 g.) at 20° for 24 hr., then 100° for 30 min., gave *dichlorotrifluoromethylphosphine* (0·379 g., 82%), b. p. 37° (Found: CF_3, 40·1; Cl, 40·8%; *M*, 171. CCl_2F_3P requires CF_3, 40·3; Cl, 41·5%; *M*, 171), as a liquid stable to mercury. Hydrolysis of the dichloro-compound (0·215 g.) with 5% aqueous sodium hydroxide (10 ml.) at 20° for 24 hr. gave fluoroform (0·0875 g., 99·5%) (*M*, 70). The reaction of the compound with water will be described later.

Ultra-violet and Infra-red Spectra.—The ultra-violet spectra were measured on Beckman DU or Unicam instruments, as solutions or as vapours in silica cells [$\varepsilon = 760 \times 22{\cdot}4 \times DT/273\,lp$, where D = optical density, T = temperature (K), l = cell length (cm.), and p = pressure of vapour (mm.)]. A Perkin–Elmer Model 21 Double Beam Instrument with rock-salt optics was employed for the infra-red spectra (annexed).

$(CF_3)_3P$		$(CF_3)_2PI$	$(CF_3)_2P{\cdot}CN$	$(CF_3)_2PCl$	$CF_3{\cdot}PI_2$ *	$CF_3{\cdot}PCl_2$	$(CF_3)_2P{\cdot}P(CF_3)_2$
4·09 (w)	7·64 (m)	4·44 (m)	4·40 (m)	4·32 } (m)	7·86 (m)	4·39 (m)	4·42 } (m)
4·35 (m)	7·83 (m)	4·51 (m)	4·56 (s)	4·42 }	8·64 (s)	5·28 (w)	4·47 }
4·46 (m)	8·13 (s)	7·85 (w)	7·84 (m)	4·46 }	8·75 (s)	7·40 (w)	5·35 (w)
5·06 (w)	8·45 (s)	7·96 (w)	8·23 (s)	5·20 (m)	9·00 (s)	7·55 (w)	7·27 (w)
5·17 (w)	8·67 (s)	8·31 (s)	8·47 (s)	7·25 (m)	9·32 (m)	7·90 (m)	7·67 (m)
5·25 (w)	8·87 (s)	8·45 (m)	8·74 (s)	7·44 (m)	13·55 (s)	8·35 (s)	7·82 (m)
5·32 (w)	9·60 (m)	8·60 (s)	8·88 (s)	7·59 (m)		8·53 (m)	8·39 (s)
5·56 (w)	9·77 (m)	8·84 (s)	9·71 (m)	7·95 (s)		8·70 (s)	8·57 (s)
5·71 (m)	10·03 (m)	8·93 (m)	10·62 (w)	8·10 (m)		8·93 (m)	8·77 (s)
5·95 (w)	10·87 (m)	9·26 (m)	10·84 (m)	8·27 (s)		9·54 (w)	8·95 (s)
6·07 (w)	11·87 (w)	9·73 (m)	11·76 (m)	8·57 (s)		10·4 (w)	9·71 (m)
6·30(w)	12·57 (w)	10·54 (w)	13·24 } (s)	8·85 (s)		12·57 (s)	10·55 (w)
6·70 (w)	13·25 (s)	11·7 (w)	13·34 }	9·75 (s)		12·82 }	11·68 (m)
7·19 (m)	13·73 (m)	12·57 (m)	14·05 (m)	10·55 (w)		12·92 }	12·55 (w)
7·43 (m)		13·34 } (s)		11·03 (w)		12·99 } (m)	13·37 (s)
		13·40 }		11·47 (w)		13·30 }	
		14·0 (w)		12·3 (s)		13·34 }	
				12·93 (w)			
				13·25 } (m)			
				13·33 }			
				13·95 (m)			

w = weak, m = medium, s = strong. Spectra of vapour unless marked * for capillary film.

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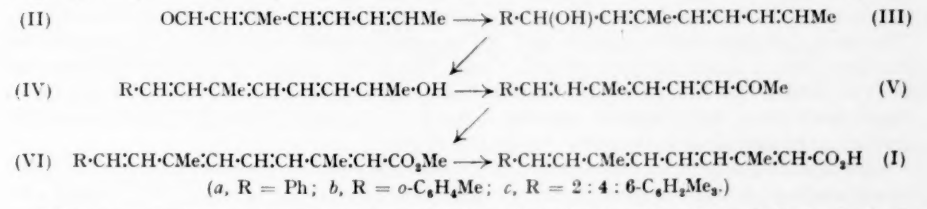
318. *Studies in the Polyene Series. Part XLVI.* The Synthesis of o-Tolyl and Mesityl Analogues of Vitamin A Acid.*

By K. R. BHARUCHA and B. C. L. WEEDON.

Syntheses of the *o*-tolyl and mesityl analogues of vitamin A acid have been achieved. When these analogues were fed as their crystalline methyl esters to rats, the *o*-tolyl compound showed no biological activity, whereas the mesityl compound exhibited slight but definite growth-promoting properties of the vitamin A type.

Some apparent anomalies in the spectra of the ester and its precursors of the mesityl series are discussed, and attributed to steric interference of resonance.

RECENTLY syntheses of the phenyl analogue (I*a*) of vitamin A acid, and the corresponding alcohol, were reported (Weedon and Woods, *J.*, 1951, 2687). As further examples of compounds of the vitamin A type possessing modified ring systems, the *o*-tolyl (I*b*) and the mesityl (I*c*) acid have now been prepared. The cyclic moiety of these acids approximates more closely to the ring system in vitamin A_1 and A_2, and, in the case of the mesityl compound, is isomeric with that found in metabolic products which are possibly of carotenoid origin (Prelog, Führer, Hagenbach, and Schneider, *Helv. Chim. Acta*, 1948, **31**, 1799).


(II) OCH·CH:CMe·CH:CH·CH:CHMe → R·CH(OH)·CH:CMe·CH:CH·CH:CHMe (III)
(IV) R·CH:CH·CMe:CH·CH:CH·CHMe·OH → R·CH:CH·CMe:CH·CH:CH·COMe (V)
(VI) R·CH:CH·CMe:CH·CH:CH·CMe:CH·CO₂Me → R·CH:CH·CMe:CH·CH:CH·CMe:CH·CO₂H (I)

(*a*, R = Ph; *b*, R = *o*-C_6H_4Me; *c*, R = 2 : 4 : 6-$C_6H_2Me_3$.)

Of the two routes developed for the synthesis of (I*a*), that based on 3-methylocta-2 : 4 : 6-trienal (II) seemed the more suitable for the introduction of substituted benzene rings.

* Part XLV, *J.*, 1953, 658.

Reaction of *o*-tolylmagnesium bromide with this aldehyde, and anionotropic rearrangement of the product (III*b*), gave the alcohol (IV*b*), which on oxidation furnished the crystalline ketone (V*b*). This with methyl bromoacetate and zinc gave, after dehydration of the initial hydroxy-ester, the ester (VI*b*) as a mixture of stereoisomers, one of which was obtained crystalline. Hydrolysis of the solid and the liquid esters yielded different crystalline isomers of the *o*-tolyl analogue (I*b*) of vitamin A acid.

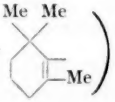
Analogous reactions were carried out with mesitylmagnesium bromide as far as the crystalline ketone (V*c*). The yields by this route of the *o*-tolyl and, especially, of the mesityl ketone were however much lower than in the phenyl series. Accordingly a new approach was examined, based on the *o*-tolyl (VII*b*) and the mesityl analogue (VII*c*) of β-ionone (VII*d*). The *o*-tolyl ketone (VII*b*) was prepared by oxidation of 4-*o*-tolylbut-3-en-2-ol (Braude, Jones, and Stern, *J.*, 1947, 1094). The mesityl ketone (VII*c*) was obtained both from the corresponding alcohol and, more conveniently, by condensation of mesitaldehyde with acetone (cf. Kohler and Blanchard, *J. Amer. Chem. Soc.*, 1935, **57**, 367). In the latter reaction 1 : 5-dimesitylpenta-1 : 4-dien-3-one was also formed.

Reformatsky reactions of 4-*o*-tolyl- (VII*b*) and 4-mesityl-but-3-en-2-one (VII*c*) with ethyl bromoacetate led to the esters (VIII*b* and *c*). Reduction of these with lithium aluminium hydride yielded the alcohols (IX*b* and *c*), which on oxidation with acetone and aluminium *tert.*-butoxide gave the ketones (V*b* and *c*) directly by condensation of the aldehydes formed initially with excess of acetone. After regeneration from the semicarbazones these ketones were obtained as crystalline solids, identical with those prepared by the alternative route described above.

Similar reactions have been used previously on a number of occasions for the extension of a polyene chain. Of particular interest is the conversion of β-ionone (VII*d*) into the C_{18} ketone (V*d*) (Milas and Harrington, *J. Amer. Chem. Soc.*, 1947, **69**, 2247), a key intermediate for the synthesis of vitamin A. Other workers (Wendler, Slates, Trenner, and Tishler, *ibid.*, 1951, **73**, 719), however, having experienced difficulty in repeating the final stage, recommended oxidation of β-ionylidene–ethanol (IX*d*) with manganese dioxide to the aldehyde (X*d*), and subsequent condensation of the latter with acetone. Similar modification of the synthesis of (V*c*) afforded no advantage.

$$\underset{\text{(VII)}}{\text{R·CH:CH·COMe}} \longrightarrow \underset{\text{(VIII)}}{\text{R·CH:CH·CMe:CH·CO}_2\text{Et}} \longrightarrow \underset{\text{(XI)}}{\text{R·CH:CH·CMe:CH·CO}_2\text{H}}$$

$$\underset{\text{(IX)}}{\text{R·CH:CH·CMe:CH·CH}_2\text{·OH}} \longrightarrow \underset{\text{(X)}}{\text{R·CH:CH·CMe:CH·CHO}} \longrightarrow \text{(V)} \longrightarrow \text{(VI)}$$

(*a*, R = Ph; *b*, R = *o*-C_6H_4Me; *c*, R = 2 : 4 : 6-$C_6H_2Me_3$; *d*, R = )

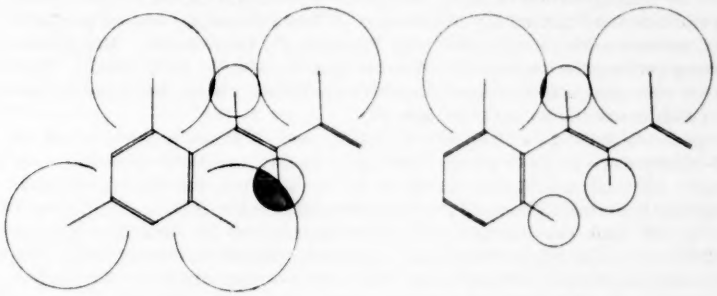
Reformatsky condensation of the ketone (V*c*) with methyl bromoacetate led to (VI*c*), one isomer of which was obtained crystalline. The solid and the liquid ester furnished two different modifications of the mesityl analogue (I*c*) of vitamin A acid.

The crystalline esters (VI*b* and *c*) were fed in arachis oil to young rats reared on a vitamin-A-free diet. No growth responses were observed with the *o*-tolyl compound at doses which would have revealed activity of the order of one-thousandth of that of vitamin A. [The phenyl analogue of vitamin A acid, fed in aqueous solution as the potassium salt, was also inactive at this dose level (Weedon and Woods, *loc. cit.*).] The mesityl compound however had about one five-hundredth of the growth-promoting activity of vitamin A. Apart from esters and ethers of vitamin A itself, this is believed to be the first aromatic derivative to exhibit activity of the vitamin A type.

Spectral characteristics of a number of the new compounds, together with those for the corresponding phenyl compounds, are given in the Table ($\lambda_{max.}$ in mμ). The *o*-tolyl and phenyl compounds exhibit very similar light-absorption properties, though the maxima are at slightly longer wave-lengths in the *o*-tolyl series, as would be expected owing to the increased methyl substitution of the chromophores. However, the additional substitution of the benzene ring in the mesityl compounds leads to marked reduction in the intensity of

absorption, and either the appearance of partial chromophores or a hypsochromic shift of $\lambda_{max.}$. These effects are believed to be similar in origin to those observed with various *cyclo*hexene derivatives (Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890; Oroshnik, Karmas, and Mebane, *J. Amer. Chem. Soc.*, 1952, **74**, 295; Braude, Bruun, Weedon, and Woods, *J.*, 1952, 1419; Bharucha and Weedon, following paper), and are attributed to steric inhibition of resonance in the mesitylene derivatives, the unsaturated side chain being displaced out of the plane of the benzene ring by an *o*-methyl group. The differences in steric interference are clearly illustrated in the Figures.* The *o*-tolyl compounds are only slightly hindered in the configuration shown, and therefore their spectral properties do not differ appreciably from those of their phenyl analogues.

o-Mesityl Series. *o-Tolyl Series.*



Interference of the type envisaged for the mesityl compounds would be expected to give rise to partial chromophores characteristic of the aromatic ring and of the polyene side chain (cf. Braude, Jones, *et al.*, *loc. cit.*); these are clearly manifested in the spectra

Compound	Phenyl series $\lambda_{max.}$	Phenyl series $\varepsilon_{max.}$	*o*-Tolyl series $\lambda_{max.}$	*o*-Tolyl series $\varepsilon_{max.}$	Mesityl series $\lambda_{max.}$	Mesityl series $\varepsilon_{max.}$
Ar·CH:CH·C(OH)·CH_3	—	—	—	—	227	9,000
	248 [1]	19,000	248 [1]	16,000	246	7,500
	251	19,500	255	16,000	251	7,500
	281	2,000	288	1,300	—	—
	291	1,550	297	700	—	—
(VII)	—	—	—	—	227	12,000
	—	—	—	—	280	11,500
	285 [2]	23,000	290	16,000	293	14,000
	—	—	—	—	301	14,000
Ar·CH:CH·CO·CH:CHAr	—	—	—	—	227	16,500
	—	—	—	—	242	13,500
	330 [3]	31,000	—	—	338	18,000
XI)	229 [4]	13,500	227 ‡	10,500	227	10,500
	—	—	—	—	290 *	14,000
	309	28,000	307	27,500	304	16,000
	—	—	312 *	24,000	312 *	14,000
V)	360 [5]	42,000	360	42,500	348	28,000
(VI)	354 *, [5]	44,500	—	—	—	—
	367	48,500	369	52,000	358	37,500
(I) †	364 [5]	56,000	367	56,000	—	—

* Inflexion. † High-melting isomer. ‡ Ethyl ester.

[1] Braude, Jones, and Stern, *J.*, 1947, 1087. [2] Lowry, Moureu, and MacConkey, *J.*, 1928, 3167. [3] Rădulescu, *Ber.*, 1931, **64**, 2243. [4] Heilbron, Jones, Julia, and Weedon, *J.*, 1949, 1823. [5] Weedon and Woods, *J.*, 1951, 2687.

of 4-mesitylbut-3-en-2-ol, the corresponding ketone (VII*c*), 1 : 5-dimesitylpenta-1 : 4-dien-3-one, and the acid (XI*c*). With 8-mesityl-6-methylocta-3 : 5 : 7-trien-2-one (V*c*) and the derived ester (VI*c*), however, the partial and full chromophore bands apparently lie sufficiently close to overlap. The observed maxima are therefore due to a summation of the

* Drawn by using covalent radii, except for hydrogen. The radius of the latter has been taken as 0·75 Å (cf. Crombie, *Quart. Reviews*, 1952, **6**, 101).

two and are consequently displaced to shorter wave-lengths by comparison with the maxima of analogous unhindered compounds (cf. Braude, Jones, *et al.*; Oroshnik *et al.*, *locc. cit.*).

The present results indicate that the carbon–carbon double bond and the aromatic ring in 2 : 4 : 6-trimethylbenzylidene derivatives are not coplanar, as has been suggested by Fuson and Bannister (*J. Amer. Soc. Chem.*, 1952, **74**, 1631) in the case of 4-mesitylbut-3-en-2-one (VII*c*). It is however noteworthy that in the latter ketone the deformation, and consequently the shielding of the β-position by the *o*-methyl groups, is insufficient to preclude conjugate addition of hydrogen cyanide to the double bond (*idem*, *loc. cit.*).

Experimental

Light absorptions were determined in alcohol unless otherwise stated. Unsaturation was determined by hydrogenation in acetic acid with a platinum catalyst unless otherwise stated. All the operations were carried out in nitrogen. Chromatography was on partially deactivated alumina (Cheeseman, Heilbron, Jones, and Weedon, *J.*, 1949, 3120). Manganese dioxide was selected from commercial sources (cf. Weedon and Woods, *J.*, 1951, 2687). Zinc used in the Reformatsky reactions was activated, immediately before use, as described by Inhoffen, Bohlmann, and Bohlmann (*Annalen*, 1950, **568**, 47).

3-*Methyl*-1-o-*tolylocta*-2 : 4 : 6-*trien*-1-*ol* (III*b*) ***and* 6-*Methyl*-8-o-*tolylocta*-3 : 5 : 7-*trien*-2-*ol*** (IV*b*).—3-Methylocta-2 : 4 : 6-trienal (24·0 g.; freshly distilled) (Weedon and Woods, *loc. cit.*) in ether (50 c.c.) was added during 1 hr. to a stirred and cooled (ice-bath) solution of *o*-tolylmagnesium bromide (from 4·3 g. of magnesium) in ether (200 c.c.). Stirring was continued for 4 hr. at 20° and the complex was then decomposed by saturated ammonium chloride solution (200 c.c.). The ethereal layer was separated, washed with water, dried (Na_2SO_4 + trace of K_2CO_3) and evaporated, giving crude 3-methyl-1-*o*-tolylocta-2 : 4 : 6-trien-1-ol (36·5 g.) as an orange mobile oil, n_D^{18} 1·5908. Light absorption : max., 270, 280, and 328 mμ; $E_{1\,cm.}^{1\%}$ = 1100, 1100, and 250 respectively. Distillation of a portion (0·7 g.) gave the alcohol as a pale yellow oil (0·34 g.), b. p. 100—110°(bath-temp.)/10^{-4} mm., n_D^{17} 1·5939 (unsaturation, in EtOAc, equiv. to 3·1 double bonds). Light absorption : max., 270 and 279 mμ; $E_{1\,cm.}^{1\%}$ = 2100 in each case.

The crude alcohol (20·0 g.) was dissolved in a 0·01M-solution of hydrochloric acid in water (320 c.c.) and acetone (680 c.c.), and kept at 20° for 14 hr. A saturated solution of sodium hydrogen carbonate was added until the pH of the mixture rose to 7—8. The bulk of the acetone was removed under reduced pressure and the product isolated with ether in the usual way. This gave a red viscous oil (19·7 g.), n_D^{20} 1·6122, which was dissolved in light petroleum (20 c.c.). The solution was cooled at −80° for 48 hr. and then allowed to warm to 0°. The yellow solid (0·6 g.) which separated was removed and had m. p. 62—65°. Crystallisation of a portion (110 mg.) from light petroleum (b. p. 60—80°) gave **6-*methyl*-8-o-*tolylocta*-3 : 5 : 7-*trien*-2-*ol*** (52 mg.) as yellow plates, m. p. 67—68° (Found : C, 83·85; H, 8·9. $C_{16}H_{20}O$ requires C, 84·15; H, 8·8%). Light absorption : max., 317 mμ; ε = 42,000.

Evaporation of the mother-liquors gave a red oil (19 g.), n_D^{18} 1·605. Light absorption : max., 270, 280, and 317 mμ; $E_{1\,cm.}^{1\%}$ = 1000, 1000, and 900 respectively, indicating a ~50% content of the rearranged alcohol.

4-o-*Tolylbut*-3-*en*-2-*one* (VII*b*).—4-*o*-Tolylbut-3-en-2-ol (50 g.) (Braude, Jones, and Stern, *J.*, 1947, 1094) in light petroleum (b. p. 40—60°) (450 c.c.) was shaken with manganese dioxide (250 g.) at 20° for 7 days. Removal of oxide and solvent, and distillation, gave the ketone (43 g.), b. p. 72—73°/5 × 10^{-4} mm., n_D^{25} 1·5805. The semicarbazone (prepared in 85% yield) had m. p. 205° (decomp.) (Braude and Sondheimer, forthcoming publication, found m. p. 206°). The ketone after regeneration from this derivative and distillation had n_D^{26} 1·5858. Light absorption : see table.

Ethyl* 2-*Methyl*-4-o-*tolylbuta*-1 : 3-*diene*-1-*carboxylate (VIII*b*).—About half of a mixture of 4-*o*-tolylbut-3-en-2-one (44·0 g.) and ethyl bromoacetate (48 g.) was added to zinc wool (18 g.) and benzene (150 c.c.). The mixture was heated under reflux until reaction commenced, and then the remainder of the ketone–ester mixture was added at such a rate (15 min. required) that gentle refluxing was maintained. Heating was then recommenced and continued for ½ hr. The mixture was cooled and shaken with N-acetic acid (400 c.c.). The benzene layer was separated, washed with saturated sodium carbonate solution, and dried (Na_2SO_4). The solution was diluted (to 500 c.c.) with the same solvent and heated under reflux for 5 hr. with toluene-*p*-sulphonic acid (0·5 g.), water being removed by azeotropic distillation. The resulting benzene solution was washed with aqueous sodium hydrogen carbonate, dried and evaporated. Dis-

tillation gave the *ester* (33·0 g.), b. p. 112—114°/3 × 10^{-3} mm., n_D^{19} 1·5961 (Found: C, 78·5; H, 8·05. $C_{15}H_{18}O_2$ requires C, 78·2; H, 7·85%). Light absorption: see Table.

Hydrolysis of the ester for 2 hr. at 60—65° with methanolic potassium hydroxide (10% w/v) gave the corresponding acid as a mixture of stereoisomers which crystallised from aqueous methanol in prisms, m. p. 138—156°.

3-*Methyl*-5-*o*-*tolylpenta*-2 : 4-*dien*-1-*ol* (IX*b*).—The preceding ester (30·0 g.) in ether (125 c.c.) was added during ½ hr. to a cooled (−50°) solution of lithium aluminium hydride (7·0 g.) in ether (200 c.c.). The mixture was then stirred for 1½ hr. at −30°. Ethyl acetate (10 c.c.) was added, to decompose any excess of hydride, and then a saturated solution of ammonium chloride (50 c.c.). The mixture was filtered and the product isolated in the usual way, giving the *alcohol* (23 g.), b. p. 70—80° (bath-temp.)/10^{-5} mm., n_D^{24} 1·6059 (Found: C, 82·55; H, 8·65. $C_{13}H_{16}O$ requires C, 82·95; H, 8·5%). Light absorption: max., 280 mμ; ε = 20,500; inflexion, 289 mμ; ε = 18,500.

6-*Methyl*-8-*o*-*tolylocta*-3 : 5 : 7-*trien*-2-*one* (V*b*).—(*a*) 6-Methyl-8-*o*-tolylocta-3 : 5 : 7-trien-2-ol (400 mg.; m. p. 62—65°) in light petroleum (b. p. 40—60°) (50 c.c.) was shaken with manganese dioxide (10 g.), at 20° for 15 hr. The mixture was filtered and the filtrate evaporated, giving a solid (400 mg.) which on crystallisation from light petroleum (b. p. 60—80°) yielded the *ketone* (200 mg.) as yellow pyramids, m. p. 83° [Found: C, 84·8; H, 8·15. $C_{16}H_{18}O$ requires C, 84·9; H, 8·0%. Unsaturation (in EtOAc; Pd) equiv. to 2·7 double bonds)]. Light absorption: see Table. The *semicarbazone* (from 52 mg. of ketone) crystallised from alcohol in yellow needles (45 mg.), m. p. 198° (decomp.) (Found: C, 71·65; H, 7·45; N, 15·2. $C_{17}H_{21}ON_3$ requires C, 72·05; H, 7·45; N, 14·85%). Light absorption: max., 361 mμ; ε = 85,000.

(*b*) The crude triene alcohol (IV*b*) (17 g.; liquid) and aluminium *tert.*-butoxide (30 g.) in a mixture of acetone (400 c.c.) and benzene (600 c.c.) were heated under reflux for 15 hr. Isolation of the product in the usual way gave an oil (17 g.), n_D^{23} 1·637, which was converted into the semicarbazone (7·3 g.), m. p. 183—188°, raised by recrystallisation from methanol to 195° (decomp.), undepressed on admixture with a specimen from (*a*).

Attempts to oxidise the crude alcohol by the manganese dioxide method were unsuccessful.

(*c*) 3-Methyl-5-*o*-tolylpenta-2 : 4-dien-1-ol (20·0 g.) and aluminium *tert.*-butoxide (40 g.) in acetone (175 c.c.) and benzene (400 c.c.) were heated under reflux for 45 hr. The crude product (24 g.) was converted into the semicarbazone, needles (9·2 g.) (from methanol), m. p. and mixed m. p. 198° (decomp.).

A mixture of the finely powdered semicarbazone (9·0 g.), light petroleum (b. p. 100—120°) (75 c.c.) and 2N-sulphuric acid (75 c.c.) was heated under reflux with vigorous stirring for 1 hr., then cooled and filtered. Recovered semicarbazone was treated in the same way. The petroleum solutions were combined, washed with water, dried (Na_2SO_4), and evaporated. The residual oil (6·2 g.), n_D^{20} 1·69—1·70, solidified and had m. p. 46—71°. A small portion recrystallised from light petroleum (b. p. 60—80°) yielded the ketone as pyramids, m. p. 82°, undepressed on admixture with a specimen from (*a*).

Methyl 2 : 6-*Dimethyl*-8-*o*-*tolylocta*-1 : 3 : 5 : 7-*tetraene*-1-*carboxylate* (VI*b*).—A mixture of the preceding ketone (m. p. 46—71°) (6·0 g.), methyl bromoacetate (freshly prepared from crystalline bromoacetic acid and diazomethane) (4·8 g.), zinc (2·0 g.), and benzene (50 c.c.) was heated under reflux until all the zinc had reacted (½ hr.). The mixture was cooled, then shaken with dilute (5% w/v) acetic acid. The benzene layer was separated, washed with water, and dried (Na_2SO_4). The resulting solution was diluted with benzene (to 250 c.c.) and then heated under reflux for 5 hr. with toluene-*p*-sulphonic acid (200 mg.). The acid was extracted with aqueous sodium hydrogen carbonate, and the benzene solution was dried and evaporated. The residue (7 g.) was chromatographed on alumina (250 g.) from light petroleum (b. p. 40—60°). The chromatogram was developed with the same solvent. The least strongly absorbed band gave an oil (3·7 g.) which partly solidified. Crystallisation from light petroleum (b. p. 60—80°) gave the *ester* (425 mg.) as yellow needles, m. p. 94° (Found: C, 80·5; H, 7·6. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·85%). Light absorption: see table. Evaporation of the mother-liquors furnished a liquid ester.

2 : 6-*Dimethyl*-8-*o*-*tolylocta*-1 : 3 : 5 : 7-*tetraene*-1-*carboxylic acid* (I*b*).—A solution of the preceding crystalline ester (31 mg.) in methanolic potassium hydroxide (1·5 c.c.; 10% w/v) was warmed for 2 hr. at 60—65° and then cooled. Water (30 c.c.) was added and the resulting suspension was acidified with aqueous (1 : 1 v/v) phosphoric acid. Isolation of the product with ether and crystallisation from methanol gave the *acid* (20 mg.) as yellow plates, m. p. 189° (decomp.) (Found: C, 80·35; H, 7·95. $C_{18}H_{20}O_2$ requires C, 80·55; H, 7·5%). Light absorption: see Table.

Similar hydrolysis of the crude liquid ester (3·2 g.) furnished an *isomer* (900 mg.) of the acid which crystallised from methanol in yellow needles, m. p. 159° (decomp.) (Found : C, 80·7; H, 7·75. $C_{18}H_{20}O_2$ requires C, 80·55; H, 7·5%). Light absorption : max., 366 mμ; ε = 53,500.

4-*Mesitylbut*-3-*en*-2-*ol*.—A solution of crotonaldehyde (8·5 g.) in ether (30 c.c.) was added during 45 min. to a stirred and cooled (ice) solution in ether (100 c.c.) of mesitylmagnesium bromide, prepared from bromomesitylene (20 g.) and magnesium (2·4 g.) (Smith, *Org. Synth.*, Coll. Vol. II, p. 360). The mixture was stirred for a further 3 hr. at 20°, the complex was decomposed by the addition of saturated ammonium chloride, and the crude product (20 g.) isolated with ether. Distillation gave a fraction (5·0 g.), b. p. 90—100° (bath-temp.)/5 × 10^{-4} mm., n_D^{21} 1·5491. Of this a portion (4·0 g.) in acetone (100 c.c.) and 0·2N-sulphuric acid (100 c.c.) was kept at 20° for 13 hr. Isolation of the product with ether gave a liquid (2·4 g.), b. p. 50—60° (bath-temp.)/10^{-5} mm., n_D^{19} 1·5500, which at 0° deposited a solid (0·51 g.), m. p. 46—48°. Crystallisation from *n*-pentane gave 4-*mesitylbut*-3-*en*-2-*ol*, m. p. 49° (Found : C, 82·45; H, 9·55. $C_{13}H_{18}O$ requires C, 82·05; H, 9·55%). Light absorption : see Table.

4-*Mesitylbut*-3-*en*-2-*one* (VII*c*) *and* 1 : 5-*Dimesitylpenta*-1 : 4-*dien*-3-*one*.—(*a*) The method used is similar to that reported recently by Fuson and Bannister (*J. Amer. Chem. Soc.*, 1952, **74**, 1631), but gives much higher yields. Sodium hydroxide (3·5 g.) was added to a solution of mesitaldehyde (38 g.) in acetone (175 c.c.) and water (20 c.c.). The mixture was stirred at 20° for 17 hr. and then poured into 2N-sulphuric acid (400 c.c.). Isolation of the product with ether gave a crude solid (43·5 g.), m. p. 49—63°. Distillation gave a product (36 g.), b. p. 108—113°/0·4 mm., m. p. 59—64°. One recrystallisation from aqueous methanol gave 4-mesitylbut-3-en-2-one as colourless needles, m. p. 67° (Kohler and Blanchard, *J. Amer. Chem. Soc.*, 1935, **57**, 367, give m. p. 67°). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in plates, m. p. 216° (Found : N, 15·4. $C_{19}H_{20}O_4N_4$ requires N, 15·25%). Light absorption in chloroform (main band only) : max., 394 mμ; ε = 23,000. The residue from the distillation solidified on cooling. Crystallisation from ethyl acetate gave 1 : 5-*dimesitylpenta*-1 : 4-*dien*-3-*one* (2·4 g.) as pale yellow needles, m. p. 170° (Found : C, 86·75; H, 8·2. $C_{23}H_{26}O$ requires C, 86·75; H, 8·25%). Light absorption : see Table.

(*b*) A solution of crystalline 4-mesitylbut-3-en-2-ol (400 mg.) in light petroleum (b. p. 40—60°; 40 c.c.) was shaken with manganese dioxide (10 g.) at 20° for 60 hr. Removal of the oxide and solvent, and crystallisation of the residue from light petroleum (b. p. 40—60°), gave the ketone (203 mg.) as needles, m. p. 67°, undepressed on admixture with a specimen from (*a*).

Ethyl 4-*Mesityl*-2-*methylbuta*-1 : 3-*diene*-1-*carboxylate* (VIII*c*).—A Reformatsky reaction with 4-mesitylbut-3-en-2-one (35 g.), ethyl bromoacetate (35 g.), and zinc (14 g.) in benzene (125 c.c.), and dehydration of the hydroxy-ester with toluene-*p*-sulphonic acid (0·5 g.) in the usual way gave the *ester* (39 g.), b. p. 60—70° (bath-temp.)/10^{-5} mm., n_D^{20} 1·5791—1·5849 (Found : C, 78·6; H, 8·55 $C_{17}H_{22}O_2$ requires C, 79·0; H, 8·6%). Light absorption : max., 228, 237, 245, 251, and 307 mμ; ε = 14,000, 10,500, 10,500, 10,500, and 18,500 respectively. Inflexions, 292 and 316 mμ; ε = 17,500 and 17,500.

Evaporation of the benzene solution before dehydration, and distillation of the residue, yielded the *hydroxy*-ester, b. p. 75—85° (bath-temp.)/10^{-5} mm., n_D^{22} 1·5191 (Found : C, 74·05; H, 8·85. $C_{17}H_{24}O_3$ requires C, 73·8; H, 8·75%). Light absorption : max., 247 and 251 mμ; ε = 9,000 and 9,000.

4-*Mesityl*-2-*methylbuta*-1 : 3-*diene*-1-*carboxylic Acid* (XI*c*).—The preceding ester (0·5 g.) was heated in methanolic potassium hydroxide (10 c.c.; 10% w/v) at 60—65° for 2 hr. Isolation of the acidic product gave a solid (430 mg.), m. p. 167—191°. Fractional crystallisation from methanol yielded one stereoisomer of the *acid* as plates (75 mg.), m. p. 207° (decomp.) (Found : C, 78·0; H, 8·05. $C_{15}H_{18}O_2$ requires C, 78·2; H, 7·85%). Light absorption : see table.

5-*Mesityl*-3-*methylpenta*-2 : 4-*dien*-1-*ol* (IX*c*).—Reduction of ethyl 4-mesityl-2-methylbuta-1 : 3-diene-1-carboxylate (36 g.) in ether at −60° with lithium aluminium hydride (7 g.) gave the *alcohol* (27·9 g.), b. p. 75—85° (bath-temp.)/10^{-5} mm., n_D^{20} 1·5860 (Found : C, 83·05; H, 9·4. $C_{15}H_{20}O$ requires C, 83·3; H, 9·3%). Light absorption : max., 227, 268, and 280 mμ; ε = 19,000, 19,000, and 20,500 respectively.

5-*Mesityl*-3-*methylpenta*-2 : 4-*dienal* (X*c*).—The preceding alcohol (3·0 g.) was shaken in light petroleum (b. p. 40—60°) (125 c.c.) with manganese dioxide (15 g.) at 20° for 96 hr. Filtration, evaporation and distillation gave the *aldehyde* (2·4 g.) as a mixture of geometrical isomers, b. p. 70—80° (bath-temp.)/10^{-5} mm., m. p. 40—53°, n_D^{21} 1·6268 (Found : C, 84·0; H, 8·6. $C_{15}H_{18}O$ requires C, 84·05; H, 8·45%). Light absorption : max., 251, 256, and 323 mμ; ε = 9,500, 9,500, and 20,000 respectively. Attempts to separate the isomers by fractional

crystallisation from *n*-pentane were unsuccessful. The *semicarbazone* crystallised from alcohol in needles, m. p. 220° (decomp.) (Found: C, 70·2; H, 7·85; N, 15·5. $C_{16}H_{21}ON_3$ requires C, 70·8; H, 7·8; N, 15·45%). Light absorption: max., 270, 280, and 325 mμ; ε = 18,000, 18,000 and 46,500 respectively.

8-*Mesityl*-6-*methylocta*-3 : 5 : 7-*trien*-2-*one* (V*c*).—(*a*) 5-Mesityl-3-methylpenta-2 : 4-dien-1-ol (12·0 g.) and aluminium *tert.*-butoxide (20 g.) in acetone (100 c.c.) and benzene (250 c.c.) were heated under reflux for 45 hr. The oily product (14·5 g.), n_D^{22} 1·635, was chromatographed on alumina (600 g.) from light petroleum (b. p. 40—60°). Elution of the least strongly adsorbed yellow band gave an oil (8·5 g.), n_D^{13} 1·652, which with excess of aqueous-methanolic semicarbazide acetate yielded a solid (7·2 g.), m. p. 211—216°. Crystallisation from alcohol gave the *semicarbazone* as yellow prisms, m. p. 217° (decomp.) (Found: N, 13·0. $C_{19}H_{25}ON_3$ requires N, 13·5%). Light absorption: max., 348 mμ; ε = 56,000.

The finely powdered semicarbazone (8·0 g.; m. p. 211—216°) was heated, with stirring, with 2N-sulphuric acid (160 c.c.) and light petroleum (b. p. 100—120°) (160 c.c.) under reflux for 45 min. The petroleum layer was separated, dried (Na_2SO_4), and evaporated to an oil (4·9 g.) which solidified. Crystallisation from light petroleum (b. p. 60—80°) gave the *ketone* as yellow plates, m. p. 89° (Found: C, 84·8; H, 8·95. $C_{18}H_{22}O$ requires C, 85·0; H, 8·7%). Light absorption: in alcohol, see Table; in *n*-hexane, max., 338 mμ; ε = 37,500.

(*b*) Sodium hydroxide (0·14 g.) in water (1 c.c.) was added to 5-mesityl-3-methylpenta-2 : 4-dienal (1·4 g.) in acetone (7 c.c.), and the mixture was kept at 20° for 21 hr. and then poured into 2N-sulphuric acid (30 c.c.). Isolation with ether yielded the crude ketone (1·25 g.), n_D^{22} 1·663. Light absorption: max., 280, 290, and 348 mμ; $E_{1\,cm.}^{1\%}$ = 430, 430, and 830 respectively. The semicarbazone, after chromatographic adsorption on alumina from chloroform, crystallised from alcohol in prisms, m. p. 217° (decomp.), undepressed on admixture with a specimen from (*a*).

(*c*) [With R. J. Woods.] Reaction of mesitylmagnesium bromide (from 8 g. of magnesium) with 3-methylocta-2 : 4 : 6-trienal (38 g.), rearrangement of the crude alcohol (68 g.) as described for the *o*-tolyl analogue, and chromatographic purification of the product on alumina from light petroleum (b. p. 40—60°), gave crude 8-mesityl-6-methylocta-2 : 4 : 6-trien-2-ol (*ca.* 19 g.). A portion (13 g.) in light petroleum (b. p. 40—60°) was oxidised with manganese dioxide, and the crude ketone converted into the semicarbazone (3·4 g.), m. p. 216°, undepressed on admixture with a specimen from (*a*). Regeneration from this derivative furnished the crystalline ketone, m. p. and mixed m. p. 89°.

Methyl 8-*Mesityl*-2 : 6-*dimethylocta*-1 : 3 : 5 : 7-*tetraene*-1-*carboxylate* (VI*c*).—A mixture of the preceding ketone (4·9 g.), zinc wool (2·0 g.), methyl bromoacetate (4·5 g.; freshly prepared), and benzene (75 c.c.) was heated under reflux until all the zinc had reacted (30 min.). Decomposition of the complex, and dehydration of the hydroxy-ester with toluene-*p*-sulphonic acid, gave an oil (6 g.) which was purified by chromatography on alumina (200 g.) from light petroleum (b. p. 40—60°). The least strongly adsorbed band yielded an oil (3·9 g.), a solution of which in light petroleum (b. p. 60—80°) (5 c.c.) deposited a solid at 0°. Crystallisation from methanol gave the *ester* as yellow plates (250 mg.), m. p. 90° (Found: C, 80·6; H, 8·5. $C_{21}H_{26}O_2$ requires C, 81·25; H, 8·45%). Light absorption: see Table. Evaporation of the mother-liquors gave a crude liquid ester (3·1 g.), n_D^{25} 1·64. Hydrolysis of the crystalline ester (30 mg.) with methanolic potassium hydroxide (10% w/v) for 2 hr. at 60° led to an acid (24 mg.), m. p. 185—195°. In another experiment the liquid ester (0·6 g.) was hydrolysed similarly and furnished another form of 8-*mesityl*-2 : 6-*dimethylocta*-1 : 3 : 5 : 7-*tetraene*-1-*carboxylic acid* (0·1 g.) which, crystallised from aqueous methanol, had m. p. 175° (decomp.) (Found: C, 81·1; H, 8·3. $C_{20}H_{24}O_2$ requires C, 81·05; H, 8·15%). Light absorption: maximum, 349 mμ; ε = 38,000.

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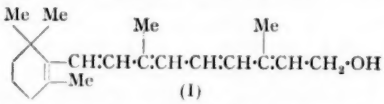
319. *Studies in the Polyene Series. Part XLVII.* The Synthesis of Two Pentaene Esters related to Vitamin A.*

By K. R. Bharucha and B. C. L. Weedon.

Syntheses of the pentaene esters (VIII*a* and *b*) are described, and the light-absorption properties of some polyenes derived from β-ionone are discussed.

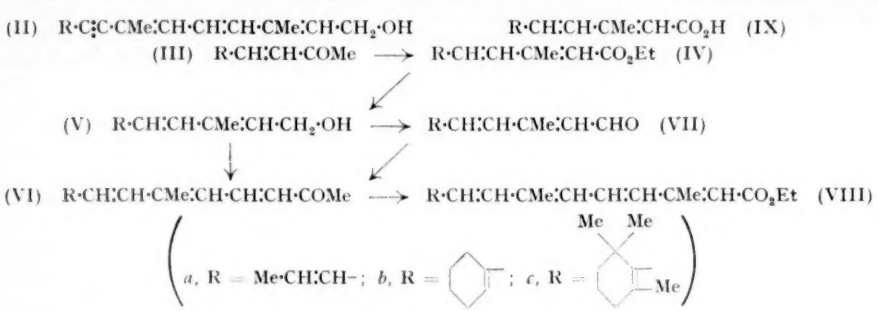
Much information has now accumulated concerning the influence on biological activity of varying the functional group and of modifying the side chain of vitamin A (I) (cf. Isler, *Chimia*, 1950, **4**, 103). Scant information is however available concerning the specificity of the ring-methyl groups (cf. Weedon and Woods, *J.*, 1951, 2687). The crystalline



(I)

alcohol (II*b*) (Cheeseman, Heilbron, Jones, and Weedon, *J.*, 1949, 3120) exhibited slight growth-promoting properties, but the presence of the acetylenic linkage in the side chain prevented an evaluation of the effect on activity of the ring modification. The investigations now reported were directed to the preparation of a polyene related to vitamin A, or the corresponding acid, but possessing an unmethylated ring system. Since β-ionone (III*c*) had been used in a number of syntheses of the natural vitamin, its lower homologue, 4-*cyclo*hexenylbut-3-en-2-one (III*b*) (Heilbron, Jones, Richardson, and Sondheimer, *J.*, 1949, 737), was selected as a suitable starting material. Model experiments were also carried out with the more readily available crotonylideneacetone (III*a*) and (see Experimental section) 5-ethylnona-3 : 5-dien-2-one.

Conversion of crotonylideneacetone (hepta-3 : 5-dien-2-one) into 3-methylocta-2 : 4 : 6-trien-1-ol (V*a*) was effected as described in Part XXXVIII (*J.*, 1951, 2687). Oxidation of the alcohol with acetone and aluminium *tert.*-butoxide gave the crystalline ketone (VI*a*) directly in 22% yield. Preliminary oxidation of the alcohol to the corresponding aldehyde



(VII*a*) (Part XXXVIII), and condensation of the latter with acetone, gave an inferior overall yield of the tetraene ketone. The structure of (VI*a*) was confirmed by catalytic hydrogenation to 6-methylundecan-2-one, which was identical with a specimen prepared by treating 5-methyldecanoic acid with methyl-lithium. A Reformatsky reaction of (VI*a*) with ethyl bromoacetate, and dehydration of the resulting hydroxy-ester, furnished the pentaene ester (VIII*a*), an acyclic analogue of the ester (VIII*c*) of vitamin A acid.

Condensation of the *cyclo*hexenylbutenone (III*b*) with ethyl bromoacetate and zinc gave, in 66% yield a mixture of triene esters, one of which (IV*b*) was obtained crystalline. Reduction of the ester with lithium aluminium hydride afforded (83%) the alcohol (V*b*)

* Part XLVI, preceding paper.

(3 : 5-dinitrobenzoate), which with acetone and aluminium *tert.*-butoxide gave the crystalline ketone (VI*b*) in 14% yield. The structure of (VI*b*) was confirmed by catalytic reduction to the known 8-*cyclo*hexyl-6-methyloctan-2-one (Heilbron, Jones, and Richardson, *J.*, 1949, 287). Oxidation of the alcohol (V*b*) with manganese dioxide gave (43%) the corresponding aldehyde (VII*b*) as a mixture of isomers, one of which was isolated by regeneration from its semicarbazone. Condensation of (VII*b*) with acetone furnished the crystalline ketone (VI*b*) in only 5% yield. A Reformatsky reaction of (VI*b*) with ethyl bromoacetate led to the pentaene ester (VIII*b*).

Unfortunately both the pentaene esters polymerised rapidly even at 0° in an inert atmosphere, and hence no significant biological assays were possible. Similar instability was also encountered in many of the intermediate compounds which, even after isolation as pure crystalline solids, decomposed rapidly. The ring-methyl groups in compounds of the vitamin A type clearly play an important rôle in stabilising the molecule.

Since the work described in this paper was completed, the preparation of dehydrovitamin A (II*c*), and the corresponding carboxylic acid, has been reported (Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094). A comparison of their biological potencies with those of related acetylenic compounds possessing modified cyclic systems (see Table 1) strongly suggests that the three ring-methyl groups of vitamin A are also necessary for high growth-promoting activity.

TABLE 1.

Substance	Method of administration *	Activity (as % of that of vitamin A)
A·C:C·CMe:CH·CH:CH·CMe:CH·CO_2H [1]	1	0·1
A·C:C·CMe:CH·CH:CH·CMe:CH·CH_2·OH [2] ...	2	0·1
B·C:C·CMe:CH·CH:CH·CMe:CH·CO_2H [3]	1	<0·1
D·C:C·CMe:CH·CH:CH·CMe:CH·CO_2H [4]	1	<0·1
E·C:C·CMe:CH·CH:CH·CMe:CH·CO_2H [4]	1	0·1
G·C:C·CMe:CH·CH:CH·CMe:CH·CO_2H [5]	2	0·5—1
G·C:C·CMe:CH·CH:CH·CMe:CH·CH_2·OH [5] ...	2	10 †
G·CH:CH·CMe:CH·CH:CH·CMe:CH·CO_2H [6]...	2	10
,, ,, ,,	1	100

A = *cyclo*hex-1-enyl; B = 4-methyl*cyclo*hex-1-enyl; D = 2-methyl*cyclo*hex-1-enyl; E = 6 : 6-dimethyl*cyclo*hex-1-enyl; G = 2 : 6 : 6-trimethyl*cyclo*hex-1-enyl.

* Fed orally to rats: (1) as an aqueous solution of sodium salt; (2) in arachis oil.

† 40% when fed as the anthraquinone-2-carboxylate.

[1] Heilbron, Jones, and Richardson, *J.*, 1949, 287. [2] Cheeseman, Heilbron, Jones, and Weedon, *J.*, 1949, 3120. [3] Toogood and Weedon, *J.*, 1949, 3123. [4] Heilbron, Jones, Lewis, and Weedon, *J.*, 1949, 2023. [5] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094. [6] Arens and van Dorp, *Nature*, 1946, **158**, 60.

TABLE 2.

	Acyclic series (*a*)		*cyclo*Hexene series (*b*)		Trimethyl*cyclo*hexene series (*c*)	
	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$
Diene ketones (III)	—	—	—	—	223 [3]	6,500
	270 [1]	28,500	281 [2]	20,800	296	10,700
Triene acids (IX)	—	—	—	—	255 [5]	13,500
	296 [4]	42,000	305 †	37,500	300	15,500
	302 *	38,000	—	—	—	—
Triene aldehydes (VII)	—	—	3140 ‡ ‡	22,000	265 [5] §	12,500
	322 [4]	30,500	323	22,000	315	16,500
Tetraene ketones (VI)	360	46,500	360	40,000	345 [6]	25,500
Pentaene esters (VIII)	352	49,000	347	>34,500	—	—
	364	49,000	364	>34,500	347 [7]	44,500

* Inflexion † Crystalline ethyl ester. ‡ Regenerated from semicarbazone; *n*-hexane solution. § *iso*Octane solution.

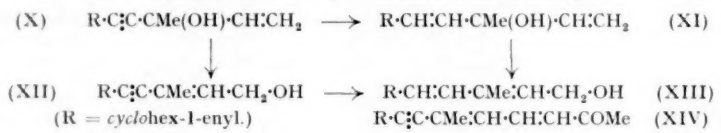
[1] Heilbron, Jones, and Richardson, *J.*, 1949, 287. [2] Heilbron, Jones, Richardson, and Sondheimer, *J.*, 1949, 737. [3] Young, Cristol, Andrews, and Lindenbaum, *J. Amer. Chem. Soc.*, 1944, **66**, 855; Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890. [4] Weedon and Woods, *J.*, 1951, 2687. [5] Wendler, Slates, Trenner, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 719. [6] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094. [7] Schwarzkopf, Cahnmann, Lewis, Swidinsky, and Wüest, *Helv. Chim. Acta*, 1949, **32**, 443.

The ultra-violet light absorptions of some of the compounds described above, and of their 2 : 6 : 6-trimethyl*cyclo*hexenyl analogues, derived from β-ionone, are collected in Table 2. The data for compounds of the acyclic and *cyclo*hexene series are in good agreement; it is however noteworthy that while the increased substitution of the chromophores results in a slight bathochromic shift of $\lambda_{max.}$ in the *cyclo*hexene derivatives (III*b*) and (IV*b*), this is not observed in the tetraene ketone (VI*b*) or the pentaene ester (VIII*b*).

Of considerable interest are the differences in the spectra of analogous compounds of the *cyclo*hexene and trimethyl*cyclo*hexene series. The light absorption properties of β-ionone (III*c*) (Braude *et al.*, *loc. cit.*), and of vitamin A (Oroshnik, Karmas, and Mebane, *J. Amer. Chem. Soc.*, 1952, **74**, 295), have been discussed previously, and shown to be consistent with the view that these two compounds possess an *s-trans*-configuration and that steric inhibition of resonance occurs, the unsaturated side chain being displaced out of the plane of the *cyclo*hexene ring by the neighbouring ring-methyl groups. This accounts in the case of β-ionone for the observed reduction in intensity of the long-wave-length band, and for the appearance of a partial chromophore band characteristic of the side chain. With vitamin A it was suggested that the observed spectrum, in which both $\lambda_{max.}$ and $\varepsilon_{max.}$ are lower than in spectra of analogous unhindered compounds, is due to a summation of the full and partial chromophore bands which lie sufficiently close to overlap.

The results now presented show that the spectra of the trimethy*cyclo*hexene derivatives (VI*c*—IX*c*) are also capable of adequate explanation on the basis of the principles summarised above. Both the tetraene ketone (VI*c*) and the pentaene ester (VIII*c*) are clearly of the vitamin A type; they exhibit single maxima which are both hypsochromically and hypochromically shifted with respect to their unhindered acyclic and *cyclo*hexene analogues. The triene acid (IX*c*) and the corresponding aldehyde (VII*c*) may be regarded as intermediate between the two extreme types represented in the above account by vitamin A and β-ionone; not only are the positions of maximal absorption slightly displaced to shorter wave-lengths, but partial chromophore bands are also apparent.

In conclusion it must be mentioned that the preparation of the triene alcohol (V*b*) and of the tetraene ketone (VI*b*), by two routes based on ethynyl*cyclo*hexene, has been claimed previously in a preliminary publication by Milas, Grossi, Penner, and Kahn (*J. Amer. Chem. Soc.*, 1948, **70**, 1292). Condensation of ethynyl*cyclo*hexene with methyl vinyl ketone gave the alcohol (X) which on partial catalytic hydrogenation to (XI) followed by allylic rearrangement, or, alternatively, by isomerisation to (XII) and subsequent catalytic reduction, was stated to yield (XIII = V*b*). However, by analogy with the isomerisation



of 3-methylocta-1 : 4 : 6-trien-3-ol (Cheeseman, Heilbron, Jones, Sondheimer, and Weedon, *J.*, 1949, 2031), an acyclic analogue of (XI), rearrangement of the latter would not be expected to give the primary alcohol (XIII) initially. Furthermore no evidence was given by the American authors in support of the selectivity claimed for the partial reduction of (X) and (XII). In this connection it may be observed that the liquid C_{15} ketone obtained in 90% yield on Oppenauer oxidation of the product which they believed to be (XIII) exhibited light absorption properties ($\lambda_{max.}$ 333 mμ; $\varepsilon = 19{,}000$) more in agreement with those of the acetylenic ketone (XIV) ($\lambda_{max.}$ 335 mμ; $\varepsilon = 23{,}000$) (Heilbron, Jones, and Richardson, *loc. cit.*) than with those of the authentic tetraene ketone reported above. This disparity between the spectral properties cannot be attributed to a difference in configuration about the double bond adjacent to the ring system. This bond is of the "hindered" type and a tetraene ketone possessing a *cis*-configuration at this position, which the American authors might conceivably have obtained by their route involving the catalytic reduction of an acetylene, would be expected to exhibit a low-intensity broad absorption band (cf. Oroshnik, Karmas, and Mebane, *J. Amer. Chem. Soc.*, 1952, **74**, 299; Garbers, Eugster, and Karrer, *Helv. Chim. Acta*, 1952, **35**, 1850).

Experimental

(See notes preceding the Experimental in Part XLV.)

6-Methylundeca-3 : 5 : 7 : 9-tetraen-2-one (VI*a*).—(*a*) A solution of 3-methylocta-2 : 4 : 6-trien-1-ol (14·0 g.) (Weedon and Woods, *J.*, 1951, 2687) and aluminium *tert.*-butoxide (40 g.) in acetone (300 c.c.) and benzene (500 c.c.) was heated under reflux for 45 hours and then cooled. The mixture was shaken with 2N-sulphuric acid, and the benzene layer was separated, washed with aqueous sodium hydrogen crabonate, dried (Na_2SO_4), and evaporated under reduced pressure. Mesityl oxide was removed by warming the crude product to 70° (bath-temp.)/1 mm. for 1 hour. A solution of the residue (18·5 g.), n_D^{20} 1·61—1·62, in *n*-hexane (*ca.* 40 c.c.) at 0° deposited a solid, m. p. 81—83°. Recrystallisation from the same solvent gave the *ketone* (4·0 g.) as yellow prisms, m. p. 85—87°, which decomposed slowly even at 0° in an inert atmosphere (Found : C, 81·8; H, 9·45. $C_{12}H_{16}O$ requires C, 81·75; H, 9·15%). Light absorption : see table. The 2 : 4-*dinitrophenylhydrazone*, crystallised from ethyl acetate, had m. p. 194° (Found : N, 15·55. $C_{18}H_{20}O_4N_4$ requires N, 15·7%). Light absorption in chloroform (main band only) : max., 424 mμ; ε = 50,000.

Evaporation of the hexane mother-liquors gave a red oil (13 g.). Light absorption : max., 264, 278, 318, and 354 mμ; $E^{1\%}_{1\,cm.}$ = 750, 740, 750, and 1280 respectively, indicating an appreciable content of the tetraene ketone, probably as a mixture of geometrical isomers. All attempts to isolate more crystalline ketone proved abortive.

(*b*) 3-Methylocta-2 : 4 : 6-trienal (6·3 g.) (*idem*, *loc. cit.*) and aluminium *tert.*-butoxide (28·8 g.) in acetone (150 c.c.) and benzene (170 c.c.) were heated under reflux for 34 hours. Decomposition of the complex and isolation of the product as in (*a*) gave an oil (9·8 g.), n_D^{25} 1·635. Distillation from a short-path still gave a yellow oil (4·62 g.), b. p. 110—120° (bath-temp.)/10^{-4} mm., n_D^{23} 1·65 (Light absorption: max., 268, 279, and 353 mμ; $E^{1\%}_{1\,cm.}$ = 530, 530, and 1480 respectively) which deposited a yellow solid when kept at 0°. Crystallisation from *n*-hexane yielded the ketone (0·45 g.), m. p. 86—87°. The 2 : 4-dinitrophenylhydrazone had m. p. 194°, undepressed on admixture with a specimen from (*a*).

6-Methylundecan-2-one.—(*a*) A solution of the preceding crystalline ketone (0·1 g.) in methanol (10 c.c.) was shaken under hydrogen in the presence of 10% palladium–charcoal (50 mg.) until absorption was complete (hydrogen absorbed, 53 c.c. at 17°/755 mm., equiv. to 3·9 double bonds). After removal of catalyst and solvent, the crude ketone was converted into the 2 : 4-dinitrophenylsemicarbazone (65 mg.), m. p. 185°, undepressed on admixture with a specimen from (*b*).

(*b*) A solution of methyl-lithium in ether (42·5 c.c.; 0·582N) was added to one of 5-methyldecanoic acid (2·2 g.) (for which the authors are indebted to Drs. R. A. Raphael and C. L. Leese) in ether (40 c.c.). The solution was shaken with 2N-sulphuric acid, dried, and evaporated, giving the ketone (1·5 g.), b. p. 130—135°/18 mm. The 2 : 4-*dinitrophenylsemicarbazone* crystallised from ethanol and had m. p. 185° (Found : C, 56·3; H, 7·1; N, 17·15. $C_{19}H_{29}O_5N_5$ requires C, 56·0; H, 7·2; N, 17·2%).

Ethyl 2 : 6-Dimethylundeca-1 : 3 : 5 : 7 : 9-pentaene-1-carboxylate (VIII*a*).—A mixture of the crystalline methylundecatetraenone (2·6 g.), ethyl bromoacetate (2·6 g.; freshly distilled), zinc wool (1·0 g.), and benzene (50 c.c.), containing traces of mercuric chloride and iodine, was heated under reflux. The reaction commenced immediately and after ½ hour the mixture was cooled. The solution was decanted from a small amount of zinc, shaken with 5% (v/v) acetic acid (60 c.c.), washed with sodium carbonate solution, and dried (Na_2SO_4). A small portion of the benzene solution (*ca.* 2—3 c.c.) was evaporated under reduced pressure and gave the hydroxy-ester as a gum. Light absorption : max., 302 and 315 mμ; $E^{1\%}_{1\,cm.}$ = 1450 and 1450.

The remainder of the benzene solution (50 c.c.) was heated under reflux for 3 hours in the presence of toluene-*p*-sulphonic acid (40 mg.) and then cooled, washed with aqueous sodium hydrogen carbonate, dried, and evaporated. The residue (3·1 g.) in benzene was poured on to a column of alumina (250 g.) and the chromatogram was developed with light petroleum (b. p. 40—60°). Elution of the least strongly adsorbed orange band yielded a viscous oil (0·5 g.). Distillation yielded the *ester* (0·2 g.), b. p. 130—140° (bath-temp.)/10^{-4} mm. (Found : C, 78·8; H, 9·3. $C_{16}H_{22}O_2$ requires C, 78·0; H, 9·0%). Light absorption : see table. It decomposed rapidly even at 0° in an inert atmosphere.

5-Ethylnona-3 : 5-dien-2-one.—A mixture of 2-ethylhex-2-enal (210 g.), acetone (375 c.c.; dried over K_2CO_3) and powdered potassium hydroxide (6·0 g.) was stirred at 20° for 12 hours, then neutralised by excess of solid carbon dioxide, and filtered. The filtrate was evaporated

and the product was extracted with ether. Distillation gave (i) recovered aldehyde (70 g.), b. p. 73—76°/20 mm., n_D^{18} 1·4556, and (ii) 5-ethylnona-3 : 5-dien-2-one (88 g.), b. p. 43—44°/10^{-2} mm., n_D^{25} 1·5073. Light absorption : max., 282 mμ; ε = 21,000. The *semicarbazone* crystallised from alcohol in needles, m. p. 157° (Found : N, 19·1. $C_{12}H_{21}ON_3$ requires N, 18·85%). Light absorption : max., 290 mμ; ε = 47,000. Inflexions, 281 and 298 mμ; ε = 37,500 and 38,000 respectively. The 2 : 4-*dinitrophenylhydrazone*, crystallised from alcohol, had m. p. 156° (Found : N, 16·15. $C_{17}H_{22}O_4N_4$ requires N, 16·15%). Light absorption in chloroform (main band only) : max., 396 mμ; ε = 36,500.

5-Ethylnonan-2-one.—A solution of the preceding ketone (5·0 g.) in methanol (30 c.c.) was shaken in the presence of palladium–calcium carbonate (0·55 g.; from 10% of $PdCl_2$) in hydrogen until absorption was complete (1240 c.c. of hydrogen absorbed at 20°/774 mm., equiv. to 1·8 double bonds). Removal of catalyst and solvent and distillation of the residue gave 5-*ethylnonan-2-one* (2·0 g.), b. p. 36°/5 × 10^{-3} mm., n_D^{21} 1·4340 (Found : C, 77·45; H, 12·65. $C_{11}H_{22}O$ requires C, 77·6; H, 13·0%). The *semicarbazone* crystallised from aqueous alcohol in needles, m. p. 97° (Found : N, 19·15. $C_{12}H_{25}ON_3$ requires N, 18·5%).

Ethyl 5-Ethyl-2-methylnona-1 : 3 : 5-triene-1-carboxylate.—A Reformatsky reaction of 5-ethylnona-3 : 5-dien-2-one (90 g.) with ethyl bromoacetate (125 g.) and zinc (42 g.) gave the hydroxy-ester (43 g.), b. p. 80—100° (bath-temp.)/6 × 10^{-4} mm., n_D^{20} 1·5107. Dehydration with toluene-*p*-sulphonic acid in the usual way yielded the *ester* (20 g.) as a mixture of isomers, b. p. 88—91°/5 × 10^{-4} mm., n_D^{21} 1·5276 (Found : C, 75·6; H, 10·25. $C_{15}H_{24}O_2$ requires C, 76·2; H, 10·25%). Light absorption : max., 280 mμ; ε = 28,500. Inflexion, 288 mμ; ε = 26,500.

Hydrolysis of the ester (0·75 g.) under reflux with methanolic potassium hydroxide (20 c.c.; 10% w/v) overnight furnished an acidic product (0·45 g.) which partly solidified. Crystallisation from pentane gave 5-*ethyl-2-methylnona-1 : 3 : 5-triene-1-carboxylic acid* (7 mg.) as needles, m. p. 103—105° (Found : C, 75·1; H, 9·5. $C_{13}H_{20}O_2$ requires C, 74·95; H, 9·7%). Light absorption : max., 300 mμ; ε = 34,500.

6-Ethyl-3-methyldeca-2 : 4 : 6-trien-1-ol.—Reduction of the preceding ester (20 g.) at −60° with lithium aluminium hydride (4·95 g.) gave the *alcohol* (7·6 g.), b. p. 84—85°/5 × 10^{-5} mm., n_D^{19} 1·5368 (Found : C, 79·75; H, 11·3. $C_{13}H_{22}O$ requires C, 80·35; H, 11·4%). Light absorption : maxima, 271 and 280 mμ; ε = 29,000 and 31,000 respectively.

Oxidation of the alcohol with aluminium *tert.*-butoxide and acetone gave 9-ethyl-6-methyltrideca-3 : 5 : 7 : 9-tetraen-2-one which was isolated as its *semicarbazone* which crystallised from methanol and had m. p. 177° (Found : N, 14·35. $C_{17}H_{27}ON_3$ requires N, 14·5%). Light absorption : max., 352, and 368 mμ; ε = 63,500 and 58,000 respectively. Inflexion, 333 mμ; ε = 48,500.

4-*cyclo*Hex-1′-enylbut-3-en-2-one (III*b*) was prepared by the method of Heilbron, Jones, Richardson, and Sondheimer (*J.*, 1949, 737). The 2 : 4-*dinitrophenylsemicarbazone* crystallised from pyridine in prisms, m. p. 232° (decomp.) (Found : N, 18·4. $C_{17}H_{19}O_5N_5$ requires N, 18·75%). Light absorption : max., 298 mμ; ε = 35,500. Inflexion, 320 mμ; ε = 25,000.

Ethyl 4-cyclo*Hex*-1′-*enyl*-2-*methylbuta*-1 : 3-*diene*-1-*carboxylate* (IV*b*).—About one-quarter of a mixture of 4-*cyclo*hex-1′-enylbut-3-en-2-one (60 g.) and ethyl bromoacetate (84 g.) freshly distilled) was added to zinc wool (32 g.), benzene (500 c.c.), and a trace of iodine. The mixture was heated under reflux until reaction commenced and the remainder of the ketone–bromoacetate solution was added at such a rate that gentle refluxing was maintained (½ hour). After being heated for a further 15 minutes, the solution was cooled, decanted from unchanged zinc (4 g.), shaken with N-acetic acid, and sodium hydrogen carbonate solution, and dried. Evaporation of a small portion and distillation of the residue (2·8 g.) gave 4-cyclo*hex*-1′-*enyl*-2-*hydroxy*-2-*methylbut*-3-*ene*-1-*carboxylate* (1·83 g.), b. p. 105°/2 × 10^{-3} mm., n_D^{24} 1·5070 (Found : C, 71·25; H, 9·4. $C_{14}H_{22}O_3$ requires C, 70·6; H, 9·25%). Light absorption : max., 234 mμ; ε = 22,500. 4-*cyclo*Hex-1′-enylbut-3-en-2-ol, which possesses the same chromophore, has max., 235 mμ; ε = 23,000 (Braude and Coles, *J.*, 1950, 2014).

The remainder of the benzene solution was diluted (to 1 l.) and heated under reflux in the presence of toluene-*p*-sulphonic acid (0·7 g.) for 5 hours; the water which separated was removed by azeotropic distillation. Isolation of the product in the usual way yielded *ethyl* 4-cyclo*hex*-1′-*enyl*-2-*methylbuta*-1 : 3-*diene*-1-*carboxylate* (58 g.) as a mixture of isomers, b. p. 104—110°/1·4 × 10^{-3} mm., n_D^{24} 1·5630—1·5738 (Found : C, 76·4; H, 9·15. $C_{14}H_{20}O_2$ requires C, 76·35; H, 9·15%). Light absorption : max., 281 and 296 mμ; ε = 22,000 and 24,000 respectively. When the fractions having $n_D^{24} > 1·5700$ were kept at 0°, a small amount of one isomer, m. p. 44°, was obtained (Found: C, 76·35; H, 9·1%). Light absorption: see table. During 12 hours at 0° in an inert atmosphere, the crystals liquefied.

Attempts to hydrolyse the ester gave irreproducible results. In one experiment the liquid ester (0·1 g.) and methanolic potassium hydroxide (10 c.c.; 10% w/v) were heated under reflux for 3 hours and gave 4-cyclo*hex*-1′-*enyl*-2-*methylbuta*-1 : 3-*diene*-1-*carboxylic acid*, yellow needles (20 mg.) (from methanol), m. p. 126° (Found : C, 75·1; H, 8·8. $C_{12}H_{16}O_2$ requires C, 74·95; H, 8·4%). Light absorption : max., 304 mμ; ε = 29,500.

5-cyclo*Hex*-1′-*enyl*-3-*methylpenta*-2 : 4-*dien*-1-*ol* (V*b*).—The preceding triene ester (50 g.; liquid) in ether (200 c.c.) was added during ½ hour to a stirred solution of lithium aluminium hydride (10·0 g.; *ca.* 80% pure) in ether (400 c.c.) at −60°. The temperature of the mixture was kept at −30° for 1½ hours and then allowed to rise to 20° during 1 hour. Ethyl acetate (8 g.) was added, to decompose the excess of hydride, followed by saturated ammonium chloride solution (75 c.c.). Isolation of the product with ether and distillation gave the *alcohol* (32 g.), b. p. 115—117°/10^{-3} mm., n_D^{24} 1·5720—1·5828 (Found : C, 80·65; H, 10·3. $C_{12}H_{18}O$ requires C, 80·85; H, 10·2%. Unsaturation, equiv. to 3 double bonds). Light absorption : max., 270 and 280 mμ; ε = 35,500 and 35,500. Inflexion, 261 mμ; ε = 29,500. The 3 : 5-*dinitrobenzoate* crystallised from acetone in orange prisms, m. p. 128° (Found : C, 61·05; H, 5·55. $C_{19}H_{20}O_6N_2$ requires C, 61·25; H, 5·4%). Light absorption : max., 237, 270, and 280 mμ; ε = 27,000, 40,000 and 40,000 respectively.

5-cyclo*Hex*-1′-*enyl*-3-*methylpenta*-2 : 4-*dienal* (VII*b*).—The preceding alcohol (3·0 g.) in light petroleum (b. p. 40—60°) (200 c.c.) was shaken with manganese dioxide (30 g.; dried over P_2O_5) at 20° for 4 hours. Removal of oxide and solvent gave an oil (2·7 g.), n_D^{26} 1·6135. Chromatography on alumina (200 g.) from benzene yielded the *aldehyde* (1·3 g.), b. p. 80—90° (bath-temp.)/10^{-4} mm., n_D^{23} 1·6250 (Found : C, 81·6; H, 8·95. $C_{12}H_{16}O$ requires C, 81·8; H, 9·15%). Light absorption in *n*-hexane : max., 294, 308, and 324 mμ; ε = 19,000, 29,000, and 24,000 respectively. Inflexion, 314 mμ; ε = 23,500. The 2 : 4-*dinitrophenylhydrazone*, crystallised from ethyl acetate, had m. p. 211° (Kofler block) (Found : N, 15·45. $C_{18}H_{20}O_4N_4$ requires N, 15·75%). Light absorption in $CHCl_3$ (main band only) : max., 415 mμ; ε = 41,500. The *semicarbazone*, crystallised from methanol, had m. p. 201° (decomp.) (Found : N, 18·05. $C_{13}H_{19}ON_3$ requires N, 18·0%). Light absorption : max., 328 and 340 mμ; ε = 42,000 and 38,000 respectively.

The yield was not improved by increasing the time of oxidation to 7 days (cf. Wendler, Slates, Trenner, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 719).

8-cyclo*Hex*-1′-*enyl*-6-*methylocta*-3 : 5 : 7-*trien*-2-*one* (VI*b*).—(*a*) 5-*cyclo*Hex-1′-enyl-3-methylpenta-2 : 4-dien-1-ol (20 g.) and aluminium *tert.*-butoxide (55 g.) in acetone (500 c.c.) and benzene (800 c.c.) were heated under reflux for 45 hours. Decomposition of the complex and isolation of the product in the usual way gave an oil (24 g.), n_D^{21} 1·628—1·630. Light absorption : max. 271, 281, 292, 352, and 362 mμ; $E_{1\,cm.}^{1\%}$ = 720, 780, 700, 680, and 680 respectively. A portion (11 g.) in light petroleum (b. p. 40—60°) was poured on alumina (300 g.) and the chromatogram was developed with benzene. The main yellow band gave the crude ketone (5·7 g.), n_D^{22} 1·650. Light absorption (main band only) : max., 354 mμ; $E_{1\,cm.}^{1\%}$ = 900. The *semicarbazone* crystallised from alcohol in yellow prisms, m. p. 206° (decomp.) (Found : N, 14·85. $C_{16}H_{23}ON_3$ requires N, 15·35%). Light absorption : max. 367 mμ; ε = 71,000. The *phenylsemicarbazone*, crystallised from aqueous pyridine, had m. p. 210° (decomp.) (Found : N, 11·85. $C_{22}H_{27}ON_3$ requires N, 12·0%). Light absorption in $CHCl_3$: max., 355 mμ; ε = 59,500. The 2 : 4-*dinitrophenylsemicarbazone*, crystallised from aqueous pyridine, had m. p. 217° (decomp.) (Found : N, 15·7. $C_{22}H_{25}O_5N_5$ requires N, 15·95%). Light absorption in $CHCl_3$: max., 350 mμ; ε = 48,500. Inflexion, 360 mμ; ε = 44,000. The first two of these derivatives decomposed rapidly even at 0° in an inert atmosphere.

A portion (0·5 g.) of the crude ketone was distilled and the distillate (0·34 g.), b. p. 80° (bath-temp.)/10^{-5} mm., collected in three equal fractions. The last of these solidified partly. Subsequently the crude product, without chromatography, was distilled in small batches (1 g.). The distillates (620 mg.), on being seeded with the solid described above partly solidified. Crystallisation from aqueous methanol gave the *ketone* (140 mg. from each batch) as yellow needles, m. p. 74—75·5° (Kofler block) (Found : C, 83·0; H, 9·3. $C_{15}H_{20}O$ requires C, 83·3; H, 9·3%). Light absorption in EtOH : see table. In *n*-hexane : max., 347 mμ; ε = 47,500. Inflexion, 353 mμ; ε = 44,500.

(*b*) 5-*cyclo*Hex-1′-enyl-3-methylpenta-2 : 4-dienal (5·8 g.) and aluminium *tert.*-butoxide (20 g.) in acetone (150 c.c.) and benzene (175 c.c.) were heated under reflux for 32 hours. Decomposition of the complex and isolation of the product as in (*a*) gave an oil (6·0 g.), n_D^{24} 1·64—1·65. Distillation gave the crude ketone (3·7 g.), b. p. 90—100° (bath-temp.)/10^{-4} mm., n_D^{21} 1·655—1·665. Light absorption : max., 280, 305, 345, and 363 mμ; $E_{1\,cm.}^{1\%}$ = 600, 740, 1160, and 1040

respectively. Inflexion: 333 mμ; $E^{1\%}_{1\,cm.}$ = 100. On seeding with a sample from (*a*), the crystalline ketone (0·4 g.), m. p. 74—76° (Kofler block), was obtained.

8-cyclo*Hexyl*-6-*methyloctan*-2-*one*.—The preceding crystalline ketone (170 mg.) was shaken in methanol (25 c.c.) in hydrogen in the presence of Adams's platinum catalyst (17 mg.) until absorption was complete (hydrogen absorbed, 69 c.c. at 22°/760 mm., equiv. to 3·6 double bonds). After removal of catalyst and solvent, the saturated ketone was converted into the semicarbazone which crystallised from aqueous methanol in plates (45 mg.), m. p. 98°, undepressed on admixture with an authentic specimen (Heilbron, Jones, and Richardson, *loc. cit.*, give m. p. 98°).

Ethyl 8-cyclo*Hex*-1′-*enyl*-2 : 6-*dimethylocta*-1 : 3 : 5 : 7-*tetraene*-1-*carboxylate* (VIII*b*).—The Reformatsky reaction between 8-*cyclo*hex-1′-enyl-6-methylocta-3 : 5 : 7-trien-2-one [2·9 g.; from route *b* above; partly crystalline; $E^{1\%}_{1\,cm.}$ (360 mμ) = *ca.* 1100, indicating a purity of *ca.* 60%], ethyl bromoacetate (2·9 g.) and zinc wool (1·1 g.) in benzene (30 c.c.), and the isolation of the product, were carried out in the usual way. Evaporation of a portion of the resulting benzene solution gave a gum which absorbed at 280—320 mμ., $E^{1\%}_{1\,cm.}$ = *ca.* 300, indicating complete reaction of the ketone.

The remainder of the benzene solution was diluted to 100 c.c. and heated under reflux for 5 hours with toluene-*p*-sulphonic acid (50 mg.). Isolation of the product gave an oil (3·2 g.), n_D^{23} 1·625. Light absorption: max., 330, 347, and 362 mμ; $E^{1\%}_{1\,cm.}$ = 560, 740, and 680 respectively. Chromatography on alumina (125 g.) from a mixture (2 : 1) of light petroleum (b. p. 40—60°) and benzene, and elution of the least strongly adsorbed, orange band yielded a viscous gum (1·6 g.), n_D^{23} 1·645—1·650. Light absorption: max., 328, 347, and 363 mμ; $E^{1\%}_{1\,cm.}$ = 820, 1070, and 780 respectively. Distillation of a portion (0·5 g.) from a short-path still gave the ester (0·22 g.) as a highly unstable viscous oil, b. p. 130—140° (bath-temp.)/10^{-4} mm. Light absorption: see table.

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320. *Studies in the Polyene Series. Part XLVIII.* The Preparation and Rearrangement of Some Dialkenylmethanols.*

By K. R. Bharucha and B. C. L. Weedon.

Reduction of but-2-yn-1-ol with lithium aluminium hydride gives *trans*-crotyl alcohol.

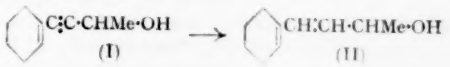
Similar reduction of alcohols obtained by reaction of ethynyl*cyclo*hexene with crotonaldehyde and crotonylideneacetone, and of the latter with pent-2-en-4-yne, gives the corresponding polyene alcohols. These rearrange readily to fully conjugated isomers, mixtures being obtained from the two unsymmetrically substituted compounds.

Previous papers in this series have described the preparation of acetylenic analogues of vitamin A and vitamin A acid from ethynyl*cyclo*hexenes. Partial hydrogenation of the triple bond in suitable intermediates in these syntheses offered promising routes to polyenes of the vitamin A type. These possibilities prompted the study now described of the reduction of some vinyl acetylenic alcohols derived from crotonaldehyde and crotonylideneacetone, and of the anionotropic rearrangement of the resulting polyene alcohols.

The method of reduction used was developed by Chanley and Sobotka (*J. Amer. Chem. Soc.*, 1949, **71**, 4140), who showed that 4-*cyclo*hex-1′-enylbut-3-yn-2-ol (I) is converted into the diene alcohol (II) in good yield with lithium aluminium hydride. Reduction of an acetylenic alcohol with this reagent would be expected, by analogy with other chemical methods (Campbell and Campbell, *Chem. Reviews*, 1942, **31**, 148), to give the *trans*-isomer of the corresponding olefin. However, to enable comparisons to be made between the polyenes prepared in the present work and those obtained previously by routes not based on acetylene (preceding paper; Braude, Bruun, Weedon, and Woods, *J.*, 1952, 1414), it was desirable to confirm the stereochemical course of the reaction. Since both *cis*- and

* Part XLVII, preceding paper.

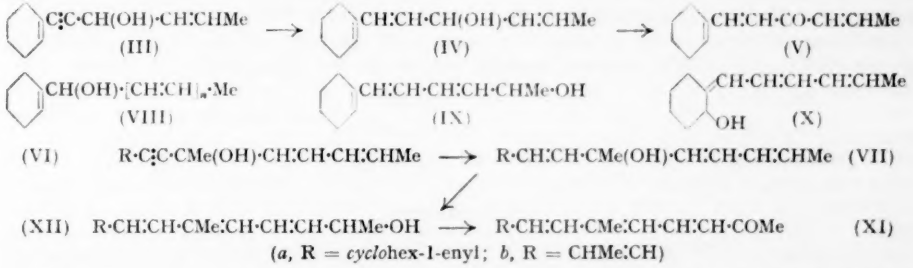
trans-forms of crotyl alcohol are readily characterised (Hatch and Nesbitt, *J. Amer. Chem. Soc.*, 1950, **72**, 727), but-2-yn-1-ol was reduced with lithium aluminium hydride; only *trans*-crotyl alcohol was detected in the product.



Similar treatment of the alcohol (III) from ethynyl*cyclo*hexene and crotonaldehyde (Heilbron, Jones, Lewis, Richardson, and Weedon, *J.*, 1949, 742) furnished a product which on oxidation (manganese dioxide) was converted in almost quantitative yield into the crystalline ketone (V). This exhibited the expected light absorption properties and on catalytic hydrogenation gave the known 1-*cyclo*hexylhexan-3-one. There is therefore no doubt that reduction of (III) occurred exclusively at the triple bond to give (IV). Similarly the alcohols (VI*a* and *b*), obtained by reaction of crotonylideneacetone with ethynyl*cyclo*hexene (Heilbron, Jones, and Richardson, *J.*, 1949, 287) and pent-2-en-3-yne, respectively, yielded the tetraenols (VII*a* and *b*).

Anionotropic rearrangement of the alcohols (IV) and (VII*a*) can conceivably take place by migration of the hydroxyl group either along the side chain or into the ring. Previously it has been found that the hydroxyl group in unsymmetrically substituted dialkenylmethanols migrates initially to the terminal carbon atom of the unsaturated system at which electron accession is the greater (Braude and Coles, *J.*, 1950, 2014; Braude and Forbes, *J.*, 1951, 1755). It was expected that the hydroxyl group of (IV) and (VII*a*), like that of the alcohols (VIII; $n = 1$ and 2) (Braude and Coles, *loc. cit.*, Braude, Bruun, Weedon, and Woods, *loc. cit.*), would migrate along the side chain almost exclusively. However rearrangement of (IV), under conditions identical with those used previously with the isomeric alcohol (VIII; $n = 1$), gave a product which had light-absorption properties in good agreement with those of (IX) but was shown to be a mixture of conjugated triene alcohols, presumably (IX) and (X).

Isomerisation of (VII*a*) also gave a mixture of alcohols, even under such mild conditions (0·001M-sulphuric acid for ½ hour) that further rearrangement of the initial product was extremely improbable (cf. Nazarov and Fisher, *Bull. Acad. Sci., U.R.S.S.*, 1948, 311; Braude and Timmons, *J.*, 1950, 2007). After Oppenauer oxidation of the mixture, and chromatographic purification, the *cyclo*hexenylmethyloctatrienone (XI*a*) was isolated as a 70% concentrate and characterised. The reason for the seemingly anomalous behaviour of (IV) and (VII*a*) on isomerisation is not apparent from existing theories on anionotropy (cf. Braude, *Quart. Reviews*, 1950, **4**, 404).



Rearrangement of the symmetrically substituted, acyclic analogue (VII*b*) of (VII*a*) gave the methylundecatetraenol (XII*b*), the structure of which was confirmed by oxidation to the known ketone (XI*b*) (preceding paper).

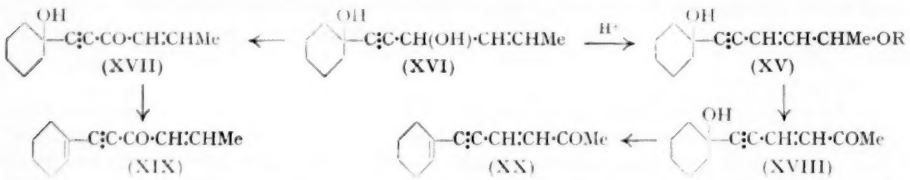
Attempts to prepare the *cyclo*hexenyl alcohol (IX) by rearrangement of the acetylenic alcohol (III) to (XIII), and reduction of the latter, were unsucessful; treatment of (XIII) with lithium aluminium hydride gave an isomer of the required trienol which, on the basis of its light absorption ($\lambda_{max.}$ 228 mμ; $\varepsilon = 23{,}000$), is believed to be formed by 1 : 4-addition of hydrogen to the vinylacetylenic system, and is provisionally assigned the allenic structure (XIV). On catalytic hydrogenation, and subsequent oxidation of the saturated alcohol,

the known 6-*cyclo*hexylhexan-2-one (semicarbazone) was obtained. Structures analogous to (XIV) have previously been proposed for products obtained by catalytic hydrogenation of symmetrical divinylacetylenes (Thompson and Shaw, *J. Amer. Chem. Soc.*, **1942**, **64**, 363).

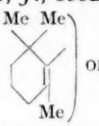
$$\text{(III)} \xrightarrow{H^+} \underset{\text{(XIII)}}{\text{R·C:C·CH:CH·CHMe(OH)}} \longrightarrow \underset{\text{(XIV)}}{\text{R·CH:C:CH·CH}_2\text{·CHMe·OH}}$$

(R = *cyclo*hex-1-enyl)

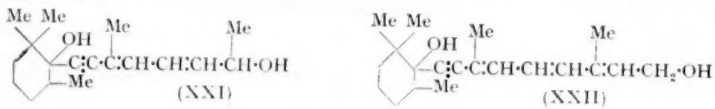
The last result indicated that for normal reduction to the corresponding olefin, an acetylene must possess a hydroxyl group on the α-carbon atom. Accordingly it seemed of interest to compare the reduction of the glycol (XV; R = H) with that of the alcohol (XIII). Reaction of the Grignard complex of ethynyl*cyclo*hexanol with crotonaldehyde gave the glycol (XVI) which on treatment with acid yielded the required conjugated



isomer (XV; R = H). The latter was also obtained directly from hex-3-en-5-yn-2-ol and *cyclo*hexanone. The structures of the glycols (XVI) and (XV) were confirmed by oxidation (manganese dioxide) to the hydroxy-ketones (XVII) and (XVIII), which on dehydration with phosphorus oxychloride in pyridine yielded the ketones (XIX) and (XX), identical with those derived from ethynyl*cyclo*hexene. When lithium aluminium hydride was used, selective reduction of the triple bond could not be achieved with either the glycol (XV; R = H) or its monotetrahydropyranyl ether (as XV), prepared by reaction of *cyclo*hexanone with 2-(tetrahydro-2-pyranyloxy)hex-3-en-5-yne.

Since these investigations were completed, the reaction of some related acetylenic alcohols and glycols with lithium aluminium hydride has been reported (Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094). Selective reduction of the triple bond was not observed with (VI; R = ) or its fully conjugated isomer. The

failure in the first case, in which the αβ-double bond was stated to be preferentially reduced, is probably due to inability of the reagent to form the necessary cyclic intermediate with the triple bond, owing to steric interference by the ring-methyl groups. Both the glycols (XXI) and (XXII) were successfully reduced to the corresponding polyenes.



Experimental

(See notes preceding the Experimental section in Part XLV.)

Reduction of Acetylenic Alcohols.—The following general method was used. A solution of the alcohol in ether was added during ½—1 hour to a stirred solution of lithium aluminium hydride (*ca.* 80% pure) in ether. The mixture was heated under reflux for 3 hours and then cooled. Ethyl acetate (*ca.* 7 c.c./g. of hydride used) was added, to decompose any excess of hydride, followed by a saturated solution of ammonium chloride (*ca.* 12 c.c./g. of hydride). The mixture was filtered and the ethereal solution was washed with water, dried (Na_2SO_4 + trace of K_2CO_3), and evaporated under reduced pressure. The various products were purified as indicated below.

trans-*Crotyl Alcohol.*—But-2-yn-1-ol (3·0 g.) in ether (25 c.c.) was reduced with lithium aluminium hydride (2·0 g.) in ether (150 c.c.). Distillation of the product gave *trans*-crotyl

alcohol (1·6 g.), b. p. 122°, n_D^{25} 1·4278 (Hatch and Nesbitt, *J. Amer. Chem. Soc.*, 1950, **72**, 727, give n_D^{25} 1·4262). The **3** : 5-dinitrobenzoate, formed in 40% yield, crystallised from benzene–light petroleum (b. p. 40—60°) (1 : 1) in needles, m. p. 68—69°, undepressed on admixture with an authentic specimen [*idem, loc. cit.*, give m. p. 70° (corr.)].

The 3 : 5-*dinitrobenzoate* of but-2-yn-1-ol crystallised from the same solvents in plates, m. p. 107° (Found : C, 50·3; H, 3·3; N, 10·55. $C_{11}H_8O_6N_2$ requires C, 50·0; H, 3·05; N, 10·6%) (*idem, loc. cit.*, give m. p. 71° for this derivative).

1-cyclo*Hex*-1′-*enylhexa*-1 : 4-*dien*-3-*ol* (IV).—1-*cyclo*Hex-1′-enylhex-4-en-1-yn-3-ol (10·0 g.) (Heilbron, Jones, Lewis, Richardson, and Weedon, *J.*, 1949, 742), in ether (75 c.c.), was reduced with lithium aluminium hydride (2·7 g.), in ether (250 c.c.), giving an oil (9·5 g.), n_D^{24} 1·5348 Light absorption : max. 237 mμ; $E_{1\,cm.}^{1\%}$ = 1340. A portion (0·52 g.) was distilled and gave the *alcohol* (0·44 g.), b. p. 60° (bath-temp.)/10^{-4} mm., n_D^{19} 1·5358 (Found : C, 81·05; H, 10·35 $C_{12}H_{18}O$ requires C, 80·85; H, 10·15%). Light absorption : max. 237 mμ; ε = 25,500 A solution of the alcohol (0·885 g.) in ethyl acetate (25 c.c.) was shaken in hydrogen in the presence of Adams's catalyst until absorption was complete. Hydrogen absorbed (346 c.c. at 20°/760 mm.) was equivalent to 2·9 double bonds.

1-cyclo*Hex*-1′-*enylhexa*-1 : 4-*dien*-3-*one* (V).—The preceding alcohol (1·7 g.; distilled) in light petroleum (b. p. 40—60°) (200 c.c.) was shaken with manganese dioxide (14 g.) at 20° for 2½ hours. Removal of oxide and solvent gave an oil (1·65 g.), n_D^{20} 1·5662, m. p. 51—54°. Crystallisation from light petroleum (b. p. 40—60°) gave the *ketone* as needles, m. p. 53—55° (Found : C, 82·0; H, 9·15. $C_{12}H_{16}O$ requires C, 81·75; H, 9·15%). Light absorption : max. 303 mμ; ε = 21,000. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in prisms, m. p. 142—144°, varying with the rate of heating (Found : N, 15·6. $C_{18}H_{20}O_4N_4$ requires N, 15·7%). Light absorption in $CHCl_3$ (main band only) : max., 404 mμ; ε = 29,500.

1-cyclo*Hexylhexan*-3-*one*.—A solution of the preceding ketone (0·304 g.) in ethyl acetate (15 c.c.) was shaken in hydrogen in the presence of Adams's catalyst (0·03 g.) until absorption was complete (128 c.c. at 18°/768 mm., equiv. to 3·1 double bonds). Removal of catalyst and solvent gave the saturated ketone (0·25 g.). The semicarbazone crystallised from aqueous methanol in needles, m. p. 126°, undepressed on admixture with an authentic specimen (*idem, loc. cit.*, give m. p. 127·5°).

Rearrangement of 1-cyclo*Hex*-1′-*enylhexa*-1 : 4-*dien*-3-*ol*.—A 0·01N-solution of hydrochloric acid and 1-*cyclo*hex-1′-enylhexa-1 : 4-dien-3-ol (4·9 g.; undistilled) in acetone (132 c.c.) and water (66 c.c.) was kept at 20° for 20 hours. The solution was saturated with salt and the product isolated with ether, giving an oil (4·1 g.), n_D^{22} 1·5690. Light absorption : max., 270 and 280 mμ; $E_{1\,cm.}^{1\%}$ = 1560 and 1560. Inflexion, 258 mμ; $E_{1\,cm.}^{1\%}$ = 1300. A portion (0·5 g.) was distilled and gave a mixture of rearranged alcohols (0·225 g.), b. p. 75—80° (bath-temp.)/10^{-4} mm., n_D^{17} 1·5738 (Found : C, 81·0; H, 10·05. $C_{12}H_{18}O$ requires C, 80·85; H, 10·15%). Light absorption : max. 270 and 280 mμ; $E_{1\,cm.}^{1\%}$ = 1680 and 1500 respectively, equiv. to ε = 30,000 and 26,500 respectively. (6-*cyclo*Hex-1′-enylhexa-3 : 5-dien-2-ol has max. at 270 and 279 mμ; ε = 33,500 and 27,500 respectively; inflexion, 259 mμ; ε = 25,000) (Braude, Bruun, Weedon, and Woods, *J.*, 1952, 1414). A solution of the mixed alcohols (1·162 g.; undistilled) in ethyl acetate (25 c.c.) was shaken in hydrogen in the presence of Adams's catalyst (0·106 g.) until absorption was complete. Hydrogen absorbed (425 c.c. at 20°/760 mm.) was equivalent to 2·7 double bonds.

The mixed alcohols (3·0 g.; undistilled) and aluminium *tert.*-butoxide (7·5 g.) in acetone (75 c.c.) and benzene (100 c.c.) were heated under reflux for 60 hours. Decomposition of the complex with dilute sulphuric acid and isolation of the product in the usual manner gave a red oil (3·5 g.) which was purified by chromatography on alumina (250 g.) from light petroleum (b. p. 40—60°). Elution of the main, yellow band gave an oil (1·15 g.), n_D^{24} 1·6000. Light absorption : max., 280 and 320 mμ; $E_{1\,cm.}^{1\%}$ = 600 and 1200 respectively. Inflexion, 292 mμ; $E_{1\,cm.}^{1\%}$ = 750. The crude product yielded a mixture of 2 : 4-dinitrophenylhydrazones which after several crystallisations from ethyl acetate had m. p. 181—194° (Found : N, 15·2. $C_{18}H_{20}O_4N_4$ requires N, 15·7%). Light absorption in $CHCl_3$ (main band only) : max, 405 mμ; $E_{1\,cm.}^{1\%}$ = 1050 (equiv. to ε = 37,500). Distillation of the crude product (0·8 g.) gave a mixture of ketones (0·223 g.), b. p. 70—80° (bath-temp.)/10^{-4} mm., n_D^{25} 1·6081, which was hydrogenated in ethyl acetate (20 c.c.) in the presence of Adams's catalyst (45 mg.) (hydrogen absorbed = 94 c.c. at 22°/762 mm., equiv. to 3 double bonds). After the catalyst and solvent had been removed, the residue was treated with methanolic semicarbazide acetate and gave a mixture of derivatives which after several crystallisations from methanol had m. p. 138—145° (50 mg.) (Found : N, 17·1. $C_{13}H_{25}ON_3$ requires N, 17·55%). The semicarbazones of 6-*cyclo*hexylhexan-2-one

(Heilbron, Jones, Lewis, Richardson, and Weedon, *loc. cit.*) and 2-*n*-hexyl*cyclo*hexanone (Braude, Bruun, Weedon, and Woods, *loc. cit.*) have m. p. 154° and 129° respectively.

1-cyclo*Hex*-1′-*enyl*-3-*methylocta*-1 : 4 : 6-*trien*-3-*ol* (VII*a*).—1-*cyclo*Hex-1′-enyl-3-methylocta-4 : 6-dien-1-yn-3-ol (4·0 g.) (Heilbron, Jones, and Richardson, *J.*, 1949, 287) (Unsaturation, equiv. to 4·8 double bonds) in ether (50 c.c.) was reduced with lithium aluminium hydride (0·88 g.) in ether (200 c.c.). Distillation of the crude product gave the *alcohol* (3·4 g.), b. p. 80—90° (bath-temp.)/10^{-4} mm., n_D^{18} 1·5458 (Found : C, 82·75; H, 10·35. $C_{15}H_{22}O$ requires C, 82·5; H, 10·15%) (Unsaturation, equiv. to 3·8 double bonds). Light absorption : max. 227 and 236 mμ; ε = 41,500 and 34,000 respectively.

Unless great care was taken to exclude, and prevent the formation of, minute traces of acid, a partly or fully rearranged product was obtained. In one experiment using half the amount of hydride given above, the product consisted almost entirely of the unchanged acetylenic alcohol.

Rearrangement of 1-cyclo*Hex*-1′-*enyl*-3-*methylocta*-1 : 4 : 6-*trien*-3-*ol*.—A solution of the unrearranged alcohol (4·9 g.) in a 0·001N-solution of sulphuric acid in acetone (370 c.c.) and water (120 c.c.) was kept at 20° for ½ hour. The solution was neutralised by the addition of aqueous sodium hydrogen carbonate, and the bulk of the acetone was removed under reduced pressure. Isolation with ether gave an oil (4·6 g.), n_D^{19} 1·6055. Light absorption (main band only) : max., 304 mμ; $E_{1\,cm.}^{1\%}$ = 1670. Distillation (accompanied by extensive polymerisation) of a small portion gave a mixture of fully conjugated alcohols, b. p. 110—115° (bath-temp.)/10^{-4} mm., n_D^{19} 1·612 (Found : C, 82·2; H, 10·3. $C_{15}H_{22}O$ requires C, 82·5; H, 10·15%). Light absorption : max., 302 and 313 mμ; $E_{1\,cm.}^{1\%}$ = 2140 and 1760 respectively, equiv. to ε = 46,500 and 38,500. Inflexion, 289 mμ; $E_{1\,cm.}^{1\%}$ = 1550.

Rearrangement with a 0·01M-solution of sulphuric acid in aqueous acetone for 1½ hours at 20° gave a similar mixture.

A solution of the mixed rearranged alcohols (1·85 g.; undistilled) in ethyl acetate (15 c.c.) was shaken in hydrogen in the presence first of 6% palladium–calcium carbonate and finally of Adams's catalyst. When absorption was complete, the catalyst and solvent were removed and the residue (1·8 g.), n_D^{20} 1·4701, in glacial acetic acid (10 c.c.) was oxidised by chromium trioxide (0·6 g.) in water (2 c.c.) and acetic acid (2 c.c.). The solution was kept overnight and the product was then isolated in the usual way, giving a mixture of saturated ketones (1·1 g.), n_D^{21} 1·4670. The mixture of 2 : 4-dinitrophenylsemicarbazones after several crystallisations from methanol had m. p. 157—161° (Found : C, 59·3; H, 7·75. Calc. for $C_{22}H_{33}O_5N_5$: C, 59·05; H, 7·45%). The 2 : 4-*dinitrophenylsemicarbazone* prepared from an authentic specimen of 8-*cyclo*hexyl-6-methyloctan-2-one (Heilbron, Jones, and Richardson, *loc. cit.*) crystallised from methanol and had m. p. 173° (Found : C, 59·3; H, 7·35. $C_{22}H_{33}O_5N_5$ requires C, 59·05; H, 7·45%). The derivative of 2-3′-methyloctyl*cyclo*hexanone had m. p. 179° (see below) which was depressed to 151—156° on admixture with the isomeric derivative.

3-*Methyloctan*-1-*ol and* 3-*Methyloctyl Bromide*.—Ethyl 2-methylheptane-1-carboxylate (12·0 g.) (Weedon and Woods, *J.*, 1951, 2687) in ether (50 c.c.) was added during ½ hour to lithium aluminium hydride (6·5 g.) in ether (200 c.c.). The mixture, which boiled gently during the addition, was stirred for 45 minutes and then cooled. Dilute sulphuric acid was added and the product was isolated with ether in the usual manner, giving 3-methyloctan-1-ol (7·8 g.), b. p. 93°/10 mm., n_D^{24} 1·4328 [Levene and Marker, *J. Biol. Chem.*, 1931, **91**, 77, give b. p. 110°/25 mm., n_D^{25} 1·4328 for the (−)-isomer].

Bromination of the alcohol (7·5 g.) with hydrobromic acid (11·0 g.; *d* 1·45) and concentrated sulphuric acid (3·4 c.c.) (cf. *Org. Synth.*, Coll. Vol. I, 2nd Edn., p. 30) gave 3-methyloctyl bromide (7·8 g.), b. p. 87°/12 mm., n_D^{21} 1·4541 (Levene and Marker, *loc. cit.*, give b. p. 104°/25 mm., n_D^{25} 1·4536, for the (+)-isomer).

2-3′-*Methyloctyl*cyclo*hexanone*.—*cyclo*Hexanone (3·5 g.) and 3-methyloctyl bromide (7·5 g.) were added rapidly to a boiling solution of potassium *tert.*-butoxide (from 1·45 g. of potassium) in *tert.*-butanol (25 c.c.). The mixture was heated under reflux for 20 minutes, then cooled and treated with excess of cold (0°) 2N-hydrochloric acid. This gave the *ketone* (2·25 g.), b. p. 84—86°/0·06 mm., n_D^{20} 1·4631 (Found : C, 80·0; H, 12·75. $C_{15}H_{28}O$ requires C, 80·3; H, 12·6%). The 2 : 4-*dinitrophenylsemicarbazone* crystallised from ethyl acetate in needles, m. p. 179° (Found : C, 59·05; H, 7·45. $C_{22}H_{33}O_5N_5$ requires C, 59·05; H, 7·45%). The *semicarbazone*, which was formed in poor yield, crystallised from aqueous methanol in plates, m. p. 124° (Found : N, 14·9. $C_{16}H_{31}ON_3$ requires N, 14·95%).

8-cyclo*Hex*-1′-*enyl*-6-*methylocta*-3 : 5 : 7-*trien*-2-*one* (XI*a*).—A solution in benzene (1800 c.c.) of aluminium *tert.*-butoxide (75 g.) and the mixture of alcohols (33 g.; undistilled) formed by rearrangement of 1-*cyclo*hex-1′-enyl-3-methylocta-1 : 4 : 6-trien-3-ol was boiled under reflux for

24 hours. Decomposition of the complex with dilute sulphuric acid and isolation of the product gave an oil which, in benzene (200 c.c.), was poured on alumina (700 g.). The chromatogram was developed with light petroleum (b. p. 40—60°) until the eluate no longer gave a positive test with Brady's reagent. The eluate (3 l.) was concentrated (to 172 c.c.) and the resulting solution (estimated to contain *ca.* 9—10 g. of conjugated tetraene C_{15} ketones by evaporation of an aliquot, and determination of the intensity at 361 mμ after dissolution of the residue in alcohol) was poured on a column of alumina (700 g.). The chromatogram was developed with the same solvent and the eluate was collected in 7 fractions. Small portions of each fraction were evaporated and the residues converted into the 2 : 4-dinitrophenylsemicarbazones. The derivative of the required ketone was readily obtained from the most strongly adsorbed fractions (4—7) which were combined (2 l.) and evaporated. Distillation of the residue (3·7 g.), n_D^{20} 1·635, gave the crude ketone (2·5 g.), b. p. 80—90° (bath-temp.)/10^{-4} mm., n_D^{25} 1·66. Light absorption: max. 350 and 363 mμ; $E_{1\,cm.}^{1\%}$ = 1340 and 1340, indicating a purity of *ca.* 70%. The 2 : 4-dinitrophenylsemicarbazone (from aqueous pyridine) had m. p. 215° (decomp.), undepressed on admixture with the derivative of 8-*cyclo*hex-1′-enyl-6-methylocta-3 : 5 : 7-trien-2-one (preceding paper). (Fractions 1—3 gave mixtures of derivatives which could not be separated.)

The ketone (0·416 g.; distilled) in ethyl acetate (20 c.c.) was shaken in hydrogen in the presence of Adams's catalyst (50 mg.) until absorption was complete (176 c.c. at 20°/765 mm., equiv. to 3·8 double bonds). Removal of catalyst and solvent gave the saturated ketone (0·385 g.) which was converted into the 2 : 4-dinitrophenylsemicarbazone. This crystallised from ethyl acetate in needles (0·23 g.), m. p. 173°, undepressed on admixture with the derivative of 8-*cyclo*hexyl-6-methyloctan-2-one but depressed by that of 2-3′-methyloctyl*cyclo*hexanone. Attempts to oxidise the mixture of tetraene alcohols by manganese dioxide were unsuccessful.

6-*Methylundeca*-2 : 4 : 9-*trien*-7-*yn*-6-*ol* (VI*b*).—Pent-2-en-4-yne (12 g.) (Eglinton and Whiting, *J.*, 1950, 3650) was added to ethylmagnesium bromide (from 3·6 g. of magnesium) in ether (300 c.c.), and the mixture was boiled under reflux for 3 hours and then cooled to 0°. Hepta-3 : 5-dien-2-one (16·5 g.) in ether (150 c.c.) was added during 3 hours and the mixture was stirred overnight at 20°. Aqueous ammonium chloride was added and the ethereal layer was separated, washed with water, dried (Na_2SO_4 + trace of K_2CO_3), and evaporated. Distillation of the residue gave the *alcohol* (18·6 g.), b. p. 55—65° (bath-temp.)/10^{-4} mm., n_D^{22} 1·5281 (Found: C, 81·35; H, 9·15. $C_{12}H_{16}O$ requires C, 81·75; H, 9·15%) (Unsaturation, equiv. to 5·3 double bonds). Light absorption: max. 227 mμ; ε = 38,500.

6-*Methylundecan*-6-*ol*.—The preceding alcohol (0·736 g.) in ethyl acetate (15 c.c.) was hydrogenated in the presence of Adams's catalyst (50 mg.) (total hydrogen absorbed, 492 c.c. at 18°/754 mm., equiv. to 4·9 double bonds). Removal of catalyst and distillation gave 6-*methylundecan*-6-*ol* (0·646 g.), b. p. 80—90° (bath-temp.)/0·5 mm., n_D^{18} 1·4403 (Found: C, 77·5; H, 14·05. $C_{12}H_{26}O$ requires C, 77·35; H, 14·05%).

6-*Methylundeca*-2 : 4 : 7 : 9-*tetraen*-6-*ol* (VII*b*).—6-Methylundeca-2 : 4 : 9-trien-7-yn-6-ol (12·0 g.) in ether (100 c.c.) was reduced with lithium aluminium hydride (3·2 g.) in ether (500 c.c.), giving the *alcohol* (9·5 g.), b. p. 79—80°/0·3 mm., n_D^{21} 1·5281 (Found: C, 80·95; H, 10·4. $C_{12}H_{18}O$ requires C, 80·85; H, 10·15%) (Unsaturation, equiv. to 3·8 double bonds. Light absorption: max. 227 mμ; ε = 44,000.

6-*Methylundeca*-3 : 5 : 7 : 9-*tetraen*-2-*ol* (XII*b*).—The preceding alcohol (1·25 g.) in a 0·01M-solution of sulphuric acid in water (32 c.c.) and acetone (91 c.c.) was kept at 20° for 90 minutes. 2N-Sodium carbonate was added to raise the pH to 7—8, the bulk of the acetone was removed under reduced pressure, and the product isolated with ether. Distillation, which was accompanied by extensive polymerisation, gave the *alcohol* (0·3 g.), b. p. 75—85° (bath-temp.)/10^{-4} mm., n_D^{20} 1·6105 (Found: C, 81·1; H, 10·15. $C_{12}H_{18}O$ requires C, 80·85; H, 10·15%). Light absorption: max. 302 and 316 mμ; ε = 48,000 and 42,000 respectively. The alcohol solidified partly at 0°.

6-*Methylundecan*-2-*ol and* 6-*Methylundecan*-2-*one*.—The preceding alcohol (1·522 g., undistilled) was hydrogenated in ethyl acetate (25 c.c.) in the presence of 7% palladium–calcium carbonate (0·3 g.), giving 6-*methylundecan*-2-*ol* (1·1 g.), b. p. 90—100° (bath-temp.)/0·3 mm., n_D^{20} 1·4386 (Found: C, 77·0; H, 13·7. $C_{12}H_{26}O$ requires C, 77·35; H, 14·05%).

The alcohol (0·9 g.) in glacial acetic acid (5 c.c.) was treated with chromium trioxide (0·4 g.) in water (1 c.c.) and acetic acid (2 c.c.), and the mixture was kept overnight. The ketonic product (0·8 g.) gave the 2 : 4-dinitrophenylsemicarbazone in good yield as needles (from alcohol), m. p. 185°, undepressed on admixture with an authentic specimen (Bharucha and Weedon, *J.*, 1953, 1571).

6-*Methylundeca*-3 : 5 : 7 : 9-*tetraen*-2-*one* (XI*b*).—A solution of 6-methylundeca-3 : 5 : 7 : 9-tetraen-2-ol (4·5 g., undistilled) and aluminium *tert.*-butoxide (10·8 g.) in benzene (300 c.c.) and acetone (140 c.c.) was heated under reflux for 24 hours. Working up in the usual way gave the crude ketone (4·3 g.), n_D^{20} 1·64—1·65. Light absorption : max., 353 mμ; $E_{1\text{ cm.}}^{1\%}$ = 1480. Inflexion, 358 mμ; $E_{1\text{ cm.}}^{1\%}$ = 1340. In *n*-hexane at 0° it deposited a solid which crystallised from the same solvent, giving 6-methylundeca-3 : 5 : 7 : 9-tetraen-2-one (0·2 g.), m. p. 85° (*idem*, *loc. cit.*, give m. p. 85—87°).

6-cyclo*Hex*-1′-*enylhexa*-4 : 5-*dien*-2-*ol* (XIV).—6-*cyclo*Hex-1′-enylhex-3-en-5-yn-2-ol (5·0 g.) (Heilbron, Jones, Lewis, Richardson, and Weedon, *loc. cit.*) in ether (40 c.c.) with lithium aluminium hydride (1·35 g.) in ether (125 c.c.) gave an oil (5·0 g.), n_D^{28} 1·5351. Light absorption : max., 229 and 270 mμ; $E_{1\text{ cm.}}^{1\%}$ = 1000 and 100 respectively. Distillation of a portion (0·5 g.) gave the *alcohol* (0·4 g.), b. p. 70—80° (bath-temp.)/10^{-4} mm., n_D^{23} 1·5358 (Found : C, 80·65; H, 10·15. $C_{12}H_{18}O$ requires C, 80·85; H, 10·15%). Light absorption : max. 228 mμ; ε = 23,000.

6-cyclo*Hexylhexan*-2-*ol and* 6-cyclo*Hexylhexan*-2-*one*.—The preceding alcohol (1·234 g.) in ethyl acetate (30 c.c.) was shaken in hydrogen in the presence of Adams's catalyst until absorption was complete (453 c.c. at 20°/761 mm., equiv. to 2·7 double bonds). Filtration and distillation gave the saturated alcohol (0·84 g.), b. p. 100—110° (bath-temp.)/1 mm., n_D^{23} 1·4680, which was oxidised in glacial acetic acid (3·5 c.c.) by the addition of a solution of chromium trioxide (0·3 g.) in acetic acid (1·5 c.c.) and water (1 c.c.). Next morning the crude ketone (0·7 g.) was isolated and converted into the semicarbazone which crystallised from methanol in plates (0·35 g.), m. p. 154°, undepressed on admixture with an authentic specimen (*idem*, *loc. cit.*, give m. p. 154°).

1-1′-*Hydroxy*cyclo*hexylhex*-4-*en*-1-*yn*-3-*ol* (XVI).—Ethynyl*cyclo*hexanol (62 g.) in benzene (100 c.c.) was added during 1½ hours to a stirred solution of ethylmagnesium bromide (from magnesium, 24 g.) in benzene (250 c.c.), and the resulting solution was warmed to 40° for 2 hours. The mixture was cooled to 0°, a solution of crotonaldehyde (45 g.) in benzene (70 c.c.) was added during ½ hour, and stirring was continued overnight at room temperature. Decomposition of the complex with ammonium chloride and isolation of the product with benzene gave the *glycol* (35 g.) as a very viscous oil, b. p. 120—130° (bath-temp.)/10^{-5} mm., n_D^{22} 1·5135 (Found : C, 74·15; H, 9·6. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·35%). The glycol exhibited no light absorption of intensity $E_{1\text{ cm.}}^{1\%} > 20$ at 220—400 mμ.

When the reaction was carried out in ether solution the glycol was obtained in 12% yield.

1-1′-*Hydroxy*cyclo*hexylhexan*-3-*ol and* 1-1′-*Hydroxy*cyclo*hexylhexan*-3-*one*.—The preceding glycol (2·89 g.) in ethyl acetate (50 c.c.), and Adams's catalyst (0·15 g.), were shaken in hydrogen until absorption was complete (925 c.c. at 17°/760 mm., equiv. to 2·6 double bonds). After removal of catalyst and solvent, distillation of the residue gave the saturated *glycol* (2·23 g.), b. p. 90—100° (bath-temp.)/10^{-4} mm., n_D^{22} 1·4830 (Found : C, 71·95; H, 11·6. $C_{12}H_{24}O_2$ requires C, 71·95; H, 12·05%). The *bis*-3 : 5-*dinitrobenzoate* crystallised from aqueous acetone in prisms, m. p. 169° (Found : C, 53·55; H, 5·0. $C_{26}H_{28}O_{12}N_4$ requires C, 53·05; H, 4·8%).

The glycol (1·69 g.) in glacial acetic acid (5 c.c.) was treated with chromium trioxide (0·56 g.) in water (2 c.c.) and acetic acid (2 c.c.). The mixture was kept overnight, then poured into cold 10% (w/v) sodium hydroxide solution (20 c.c.). The product was isolated by extraction with ether. Distillation yielded 1-1′-*hydroxy*cyclo*hexylhexan*-3-*one* (0·8 g.), b. p. 90—100° (bath-temp.)/10^{-5} mm., n_D^{20} 1·4782 (Found : C, 72·85; H, 11·5. $C_{12}H_{22}O_2$ requires C, 72·65; H, 11·2%).

1-1′-*Hydroxy*cyclo*hexylhex*-4-*en*-1-*yn*-3-*one* (XVII).—1-1′-Hydroxy*cyclo*hexylhex-4-en-1-yn-3-ol (5·7 g.) in acetone (300 c.c.) was shaken with manganese dioxide (75 g.) at 20° for 6 hours. The mixture was filtered and the solution evaporated under reduced pressure to a viscous oil (5·7 g.), n_D^{20} 1·5264. Light absorption : max. 228, 236, and 242 mμ; $E_{1\text{ cm.}}^{1\%}$ = 620, 575, and 450 respectively.

Chromatography of the crude product on alumina (*ca.* 250 g.) from benzene solution and distillation gave the *hydroxy-ketone* (3·73 g.), b. p. 100° (bath-temp.)/10^{-5} mm., n_D^{22} 1·5268 (Found : C, 74·9; H, 8·45. $C_{12}H_{16}O_2$ requires C, 74·95; H, 8·4%). Light absorption : max. 227 mμ; $E_{1\text{ cm.}}^{1\%}$ = 620; ε = 12,000. Inflexion, 236 mμ; $E_{1\text{ cm.}}^{1\%}$ = 580; ε = 11,000. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in bright prisms, m. p. 166° (Found : N, 14·9. $C_{18}H_{20}O_5N_4$ requires N, 15·05%). Light absorption in $CHCl_3$ (main band only) : max., 386 mμ; ε = 35,000.

1-cyclo*Hex*-1′-*enylhex*-4-*en*-1-*yn*-3-*one* (XIX).—Phosphorus oxychloride (1·0 g.) in toluene (4 c.c.) and pyridine (4 c.c.) was added dropwise at 0° to a solution of the preceding hydroxy-ketone (1·0 g.) in toluene (4 c.c.). The mixture was warmed at 70—80° for 1 hour, then cooled, and ice was added. Isolation in the usual manner and distillation of the product gave the *ketone* (0·5 g.) as an unstable oil, b. p. 55—65° (bath-temp.)/10^{-4} mm., n_D^{17} 1·5683 (Found : C, 82·3; H,

8·3. $C_{12}H_{14}O$ requires C, 82·7; H, 8·1%). Light absorption: max., 280 and 304 mμ; ε = 12,000 and 15,000 respectively. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in orange prisms, m. p. 176°, undepressed on admixture with a specimen prepared from the product of manganese dioxide oxidation of 1-*cyclo*hex-1′-enylhex-4-en-1-yn-3-ol (Heilbron, Jones, Lewis, Richardson, and Weedon, *loc. cit.*) (Found: N, 15·85. $C_{18}H_{18}O_4N_4$ requires N, 15·8%). Light absorption in $CHCl_3$ (main band only): max. 397 mμ; ε = 31,500.

The hydroxy-ketone was recovered after being heated for 1 hour in benzene solution containing a trace of toluene-*p*-sulphonic acid.

6-1′-*Hydroxy*cyclo*hexylhex*-3-*en*-5-*yn*-2-*ol* (XV; R = H).—(*a*) 1-1′-Hydroxy*cyclo*hexylhex-4-en-1-yn-3-ol (3·0 g.) was shaken with a trace of quinol and 5% (w/v) sulphuric acid (30 c.c.) at room temperature for 36 hours. Isolation of the product with ether and distillation gave the *glycol* (1·8 g.), b. p. 120—130° (bath-temp.)/10^{-4} mm., n_D^{20} 1·5321 (Found: C, 73·95; H, 9·5. $C_{12}H_{18}O_2$ requires C, 74·15; H, 9·35%). Light absorption: max., 227 mμ; ε = 17,500; inflexion, 233 mμ; ε = 16,000.

(*b*) A solution of the di-Grignard complex of hex-3-en-5-yn-2-ol (40 g.) (Heilbron, Jones, Smith, and Weedon, *J.*, 1946, 57) in benzene (300 c.c.) was prepared in the usual manner, then cooled to 0°. *cyclo*Hexanone (45 g.) in benzene (75 c.c.) was added dropwise during ½ hour. Stirring was continued overnight at 20° and the solution poured into a saturated solution of ammonium chloride (200 g.) in water. Isolation in the usual manner gave the glycol (40 g.), b. p. 120—130° (bath-temp.)/10^{-4} mm., n_D^{15} 1·529. Light absorption: max. 227 mμ; ε = 12,000. Inflexion 234 mμ; ε = 10,000. Active hydrogen (Zerewitinoff): the glycol (50·6 mg.) yielded 13·2 c.c. of methane at 15°/747 mm., equiv. to 2·1 atoms of active hydrogen per mol.

6-1′-*Hydroxy*cyclo*hexyl-hexan*-2-*ol and -hexan*-2-*one*—The preceding glycol (4·324 g.) in ethyl acetate (50 c.c.) was shaken in hydrogen in the presence of Adams's catalyst (0·15 g.) until absorption was complete (1454 c.c. at 18°/760 mm., equiv. to 2·8 double bonds). The solvent and catalyst were removed and the residue was distilled, giving the saturated *glycol* (3·6 g.), b. p. 100—110° (bath-temp.)/10^{-5} mm., n_D^{18} 1·4870 (Found: C, 72·25; H, 11·9. $C_{12}H_{24}O_2$ requires C, 71·95; H, 12·05%). The *bis*-3 : 5-*dinitrobenzoate*, crystallised from acetone, had m. p. 133—135° (Found: C, 53·45; H, 5·1. $C_{26}H_{28}O_{12}N_4$ requires C, 53·05; H, 4·8%).

The saturated glycol (1·37 g.) in glacial acetic acid (5 c.c.) was treated with chromium trioxide (0·46 g.) in water (2 c.c.) and glacial acetic acid (2 c.c.). The mixture was kept at 20° overnight, then poured into aqueous sodium hydroxide (20 c.c.; 10% w/v). Isolation of the product with ether and distillation gave the *hydroxy-ketone* (0·85 g.), b. p. 90—100° (bath-temp.)/10^{-5} mm., n_D^{21} 1·4801 (Found: C, 72·55; H, 11·15. $C_{12}H_{22}O_2$ requires C, 72·65; H, 11·2%). The 2 : 4-*dinitrophenylsemicarbazone*, crystallised from alcohol, had m. p. 184° (decomp.) (Found: N, 16·2. $C_{19}H_{27}O_6N_5$ requires N, 16·6%).

6-1′-*Hydroxy*cyclo*hexylhex*-3-*en*-5-*yn*-2-*one* (XVIII).—6-1′-Hydroxy*cyclo*hexylhex-3-en-5-yn-2-ol (8·0 g.) in acetone (300 c.c.) was shaken with magnanese dioxide (75 g.) at 20° for 6 hours. Removal of oxide and solvent gave an oil (8·0 g.), n_D^{19} 1·5285. The ketonic product was separated by means of the Girard reagent P (cf. Girard and Sandulesco, *Helv. Chim. Acta*, 1936, **19**, 1095) and distilled, giving the *hydroxy-ketone* (1·3 g.), b. p. 100—110° (bath-temp.)/10^{-5} mm., n_D^{19} 1·5390 (Found: C, 74·9; H, 8·6. $C_{12}H_{16}O_2$ requires C, 74·95; H, 8·4%). Light absorption: max., 268 mμ; ε = 19,000. Inflexions, 258 and 272 mμ; ε = 17,500 and 17,500. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in red prisms, m. p. 184° (Found: C, 57·75; H, 5·55; N, 14·65. $C_{18}H_{20}O_5N_4$ requires C, 58·05; H, 5·4; N, 15·05%). Light absorption in $CHCl_3$ (main band only): max., 382 mμ; ε = 34,500.

The same yield of hydroxy-ketone was obtained by carrying out the above oxidation in a mixture (10 : 1) of light petroleum (b. p. 40—60°) and dioxan.

6-cyclo*Hex*-1′-*enylhex*-3-*en*-5-*yn*-2-*one* (XX).—Phosphorus oxychloride (1·2 g.) in toluene (5 c.c.) and pyridine (4 c.c.) was added dropwise at 0° to a solution of the preceding hydroxy-ketone (1·0 g.) in toluene (4 c.c.). The mixture was warmed at 70—80° for 1½ hours. Isolation of the product in the usual way gave an oil (0·5 g.), b. p. 70—75° (bath-temp.)/10^{-3} mm., n_D^{20} 1·5791, which with alcoholic semicarbazide acetate gave the semicarbazone of 6-*cyclo*hex-1′-enylhex-3-en-5-yn-2-one, yellow plates (0·44 g.) (from methanol), m. p. 186° (Heilbron, Jones, Lewis, Richardson, and Weedon, *loc. cit.*, give m. p. 185°). Light absorption: max., 310 mμ; ε = 43,500. Inflexion, 320 mμ; ε = 37,000. The semicarbazone (0·2 g.) was converted into the 2 : 4-*dinitrophenylhydrazone* which crystallised from ethyl acetate in needles (0·15 g.), m. p. 181—183°, undepressed on admixture with a specimen made from the authentic ketone (Found: N, 16·2. $C_{18}H_{18}O_4N_4$ requires N, 15·8%). Light absorption in $CHCl_3$ (main band only): max., 398 mμ; ε = 37,000.

The hydroxy-ketone was recovered after ½ hour's heating in benzene containing a trace of toluene-*p*-sulphonic acid.

2-(*Tetrahydro-2-pyranyloxy*)*hex-3-en-5-yne*.—A few drops of concentrated hydrochloric acid were added to a mixture of hex-3-en-5-yn-2-ol (32 g.) and dihydropyran (28 g.), the temperature being kept at 20°. After 3 hours the mixture was diluted with ether, and the solution was washed with aqueous sodium hydroxide (10% w/v), dried, and evaporated. Distillation gave the *tetrahydropyranyl ether* (40 g.), b. p. 99—100°/10 mm., n_D^{23} 1·4771, which gave a white precipitate with ammoniacal silver nitrate (Found: C, 72·9; H, 8·95. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·95%). Light absorption: max., 227 mμ; ε = 16,500.

6-1′-*Hydroxy*cyclo*hexyl*-2-(*tetrahydro-2-pyranyloxy*)*hex-3-en-5-yne*.—The preceding tetrahydropyranyl ether (6·5 g.) in ether (3 c.c.) was added during 15 minutes to a stirred solution of sodamide (prepared from 0·8 g. of sodium; cf. Vaughn, Vogt, and Nieuwland, *J. Amer. Chem. Soc.*, 1934, **56**, 2120) in liquid ammonia (100 c.c.). After 3 hours, *cyclo*hexanone (3·5 g.) in ether (5 c.c.) was added dropwise and stirring was continued for 3½ hours. Ammonium chloride (2 g.) was added and the ammonia was allowed to evaporate overnight. The residue was extracted with ether, and the ethereal solution was washed with water and dried (Na_2SO_4). Distillation gave the *hydroxy-acetal* (4·0 g.), b. p. 105—115° (bath-temp.)/10^{-4} mm., n_D^{23} 1·5155 (Found: C, 73·7; H, 9·1. $C_{17}H_{26}O_3$ requires C, 73·35; H, 9·4%) (Unsaturation, equiv. to 3 double bonds). Light absorption: max., 227 mμ; ε = 20,000. Inflexion, 236 mμ; ε = 14,000. Active hydrogen (Zerewitinoff): the hydroxy-acetal (0·121 g.) gave 11·5 c.c. of methane at 15°/750 mm., equiv. to 1·1 atoms of active hydrogen per mol.

Reaction in ethereal solution of the tetrahydropyranyl ether with *cyclo*hexanone, by the Grignard method, gave 6-1′-hydroxyl*cyclo*hexylhex-3-en-5-yn-2-ol. The structure of the product was confirmed by Zerewitinoff determination (2·05 atoms of active hydrogen per mol.), and by oxidation (manganese dioxide) to the hydroxy-ketone (2: 4-dinitrophenylhydrazone, m. p. and mixed m. p. 185°).

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321. *The Addition of Free Radicals to Unsaturated Systems. Part III.* Chlorotrifluoroethylene.†*

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The direction of addition of the trifluoromethyl radical to chlorotrifluoroethylene has been established. Photochemical reaction of trifluoroiodomethane with chlorotrifluoroethylene yields only compounds of general formula $CF_3{\cdot}[C_2ClF_3]_n{\cdot}I$, the value of n depending on the ratio of reactants, with a maximum of 85% of the compound where $n = 1$. The constitution of the compound with $n = 1$ is unambiguously shown to be exclusively $CF_3{\cdot}CF_2{\cdot}CFClI$, this contradicting Henne and Kraus's results (*J. Amer. Chem. Soc.*, 1951, **73**, 1791). This compound yields perfluorohex-3-ene by intermolecular removal of iodine followed by dechlorination, and $CF_3{\cdot}CF{:}CHF$ by reduction followed by dehalogenation; mechanisms are suggested for these reactions. The compounds where $n = 1$—5 have been separated and characterised, and their constitution as $CF_3{\cdot}[CF_2{\cdot}CFCl]_n{\cdot}I$ proved. Polychlorotrifluoroethylene (Kel-F) is thus formed by head-to-tail polymerisation of chlorotrifluoroethylene. Ultra-violet and infra-red spectra are presented and their diagnostic value is discussed.

The direction of addition of a free radical to chlorotrifluoroethylene cannot be predicted in a satisfactory manner by any of the current theories; so, as part of a systematic investigation on free-radical addition reactions, the attack of a trifluoromethyl radical

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has been studied. Photolysis of trifluoroiodomethane was used for preparation of the trifluoromethyl radical; the reasons for the choice of this radical and the basic assumptions made in this type of study have been outlined earlier (Part I, *J.*, 1952, 2504).

Trifluoroiodomethane and chlorotrifluoroethylene react smoothly on exposure to ultraviolet light and yield products of general formula $CF_3{\cdot}[C_2ClF_3]_n{\cdot}I$. The value of n depends on the relative amounts of the reactants and to aid determination of orientation conditions have been chosen so that the compound where $n = 1$ is obtained in high yield (*ca.* 85%).

The compound where $n = 1$ might be (I) or (II), but the following evidence shows that only (I) is formed (to the extent of at least 95%).

(I) $CF_3{\cdot}CF_2{\cdot}CFClI$ $CF_3{\cdot}CFCl{\cdot}CF_2I$ (II)

The product readily liberates iodine on exposure to light, and photochemical chlorination gives a high yield of the dichloride (III): (II) would have given (IV) by this procedure. Compounds (III) (b. p. 35°, n_D^{20} 1·305) and (IV) (b. p. 34·7°, n_D^{20} 1·3029) cannot be distinguished by boiling point or refractive index, but comparison of the infra-red spectrum of (III) with that of a known sample of (IV), prepared from hexafluoropropene and chlorine, readily distinguishes the two isomers.* Further, with zinc and ethanol (IV) readily yields hexafluoropropene, whereas (III) does not (see below).

$CF_3{\cdot}CF_2{\cdot}CFCl_2$ (III; C.S. 36) $CF_3{\cdot}CFCl{\cdot}CF_2Cl$ (IV; C.S. 37) $CF_3{\cdot}CF_2{\cdot}CHFCl$ (V; C.S. 38) $C_2F_5{\cdot}CFCl{\cdot}CFCl{\cdot}C_2F_5$ (VI; C.S. 39)

With bromine trifluoride, a vigorous fluorinating agent found very suitable for the replacement of iodine by fluorine in polyhalogeno-iodides, the compound where $n = 1$ yields 1-chloroheptafluoropropane, identical with a specimen prepared from heptafluorobutyric acid (Haszeldine, *J.*, 1951, 584; 1952, 4259) by comparison of infra-red spectra (C.S. 40.) This again establishes the configuration as (I), since (II) would have yielded 2-chloroheptafluoropropane.

The compound (I; $n = 1$) (C.S. 41) undergoes a complex reaction with zinc and ethanol, mainly replacement of iodine by hydrogen, to give (V), but spectroscopic examination in the 5·5—6·5-μ region reveals that two olefins, neither being hexafluoropropene, are formed in *ca.* 10% yield. Removal of the unsaturated material by treatment with chlorine left (V), whose infra-red spectrum proves that hydrogen is present (typical sharp C–H stretching absorption at 3·34 μ). The dichloride (III) fails to liberate hexafluoropropene on treatment with zinc and ethanol, which proves that (IV) is absent: (IV) gave more than 90% of hexafluoropropene under identical conditions. Somewhat surprisingly, (III) is not inert to zinc and ethanol, and like (I) yields mainly (V); spectroscopic examination shows that only one of the two olefins is present.

The unsaturated material formed from (I) yields two dichlorides. The first, $C_6F_{12}Cl_2$, b. p. 111°, is shown to be 3 : 4-dichlorododecafluorohexane (VI) by means of its infra-red

$CF_3{\cdot}CFCl{\cdot}CHFCl$ (VII) $C_2F_5{\cdot}CF{:}CF{\cdot}C_2F_5$ (VIII; C.S. 42) $CF_3{\cdot}CF{:}CHF$ (IX; C.S. 43) $CF_3{\cdot}CF{:}CFCl$ (X)

spectrum; the second is 2 : 3-dichloro-1 : 1 : 1 : 2 : 3-pentafluoropropane (VII), identified *via* its dechlorination product (IX). These compounds clearly arise from (I), (*a*) by a coupling reaction, $CF_3{\cdot}CF_2{\cdot}CFClI \xrightarrow{Zn\text{–}EtOH} [CF_3{\cdot}CF_2{\cdot}CFCl]_2 \xrightarrow{Zn\text{–}EtOH} C_2F_5{\cdot}CF{:}CF{\cdot}C_2F_5$, and (*b*) by reduction to (V) followed by removal of chlorine and fluorine. The dichloride (VI) was synthesised by photolysis of (I) in the presence of mercury:

$$CF_3{\cdot}CF_2{\cdot}CFClI \xrightarrow{h\nu,\ Hg} CF_3{\cdot}CF_2{\cdot}CFCl{\cdot} \longrightarrow (VI)$$

Dechlorination of (VI) with zinc and ethanol yields perfluorohex-3-ene (VIII) {(II) would have given $[CF_3{\cdot}CFCl{\cdot}CF_2]_2$ by this sequence}. The infra-red spectrum of (VIII) has a C=C stretching vibration at 5·84 μ, showing that at least some of the *cis*-isomer is present; the marked shift to longer wave-length of the C=C vibration relative to that in octafluorobut-2-ene (5·77 μ; Haszeldine, *J.*, 1952, 4423) can be attributed to the replace-

* Copies of infra-red spectra designated by C.S. nos. have been deposited with the Chemical Society (cf. *Proc.*, 1952, 164), and photocopies may be obtained from the General Secretary. The C.S. no. must be cited in such requests.

ment of the trifluoromethyl group by the heavier and less electronegative pentafluoroethyl group. Comparison of the spectrum of (VIII) with the spectra of the materials obtained by reaction of (I) or (III) with zinc and ethanol showed that (VIII) was formed from (I) but not from (III). This is not unexpected, since the coupling reaction to give (VI), which must precede the formation of (VIII), will clearly occur much more readily with (I), which contains a carbon–iodine bond, than with (III), which contains a carbon–chlorine bond.

The coupling of compounds containing carbon–iodine bonds can be achieved photochemically, mercury being used to remove iodine atoms, or by the use of zinc and dioxan, which favours intermolecular dehalogenation rather than intramolecular dehalogenation or reduction (Haszeldine, *J.*, 1952, 4423). Application of the zinc–dioxan technique to (I) gave (VIII), with only traces of (V). It is emphasised that, to get preferential coupling instead of reduction, the reaction with zinc and dioxan must be carried out at as low a temperature as possible. After coupling has occurred, dehalogenation of the new compound can be effected *in situ* by raising the temperature to the boiling point:

$$\text{(I)} \xrightarrow[20^\circ]{\text{Zn-dioxan}} \text{(VI)} \xrightarrow[100^\circ]{\text{Zn-dioxan}} \text{(VIII)}.$$

The isolation of (IX) after reaction of zinc and ethanol with (III) or (V) shows that its formation from (I) proceeds *via* (V). This is the first recorded instance of the removal of fluorine from a CF_2 group under such relatively mild conditions. Perfluoropropane and 1-chloroheptafluoropropane are stable to zinc and ethanol at 300°, but heptafluoro-1-iodopropane yields hexafluoropropene and heptafluoropropane at 200°. If the first step of the dehalogenation reaction $\cdot CF_2\cdot CFXX' \longrightarrow \cdot CF{:}CFX'$ involves loss of X as X^-, or conversion of $\cdot CF_2\cdot CFXX'$ into $\cdot CF_2\cdot CFX'\cdot ZnX$, then the ease of reaction will clearly be in the order X = I > Br > Cl > F. The nature of X′ is also important in so far as it facilitates loss of X as X^-. The dehalogenation reaction should proceed most readily with X = H > Br > Cl > F, and this is in accord with the absence of $CF_3\cdot CF{:}CFCl$ as a reaction product of (I) or (III) with zinc and ethanol. Dehalogenation does not occur until the terminal CHFCl group has been formed by reduction. Pentafluoropropene reacts readily with chlorine, to give the dichloride (VII). That the pentafluoropropene obtained from (I) contains no hexafluoropropene is shown by examination of infra-red spectra.

The boiling points of the fluoropropenes (Table 1) show that concentration of fluorine atoms at one end of the molecule, or on the minimum number of carbon atoms, gives the lower boiling point in any particular pair of isomers (cf. $CF_3\cdot CF{:}CH_2$, $CF_3\cdot CH{:}CHF$; $CF_3\cdot CH{:}CF_2$, $CF_3\cdot CF{:}CHF$); this effect has been noted earlier with bromo- and chlorofluoropropenes (Haszeldine, *J.*, 1951, 2495).

TABLE 1. *Boiling points.*

$CF_3\cdot CF{:}CF_2$ [1]	−29°	$CF_3\cdot CH{:}CHF$ [3]	−16°	$CF_3\cdot CF{:}CHF$ [2]	−18·5°
$CF_3\cdot CF{:}CH_2$ [1]	−28·3°	$CF_3\cdot CH{:}CF_2$ [1]	−21·0°	$CF_3\cdot CH{:}CH_2$ [4]	−22°

[1] Henne and Waalkes, *J. Amer. Chem. Soc.*, 1946, **68**, 496. [2] This paper. [3] Haszeldine and Steele, *J.*, 1953, 1199. [4] Haszeldine, *J.*, 1951, 2495.

The evidence summarised above clearly establishes the orientation in the addition of trifluoroiodomethane to chlorotrifluoroethylene. With a chain mechanism similar to that proposed for the interaction of trifluoroiodomethane and tetrafluoroethylene (Haszeldine, *J.*, 1949, 2856), *viz.*,

$$CF_3I \xrightarrow{h\nu} CF_3\cdot + I\cdot.$$

Initiation: $CF_3\cdot + CF_2{:}CFCl \longrightarrow CF_3\cdot CF_2\cdot CFCl\cdot$

Propagation: $CF_3\cdot CF_2\cdot CFCl\cdot + CF_2{:}CFCl \longrightarrow CF_3\cdot CF_2\cdot CFCl\cdot CF_2\cdot CFCl\cdot$ etc.

Transfer: $CF_3\cdot CF_2\cdot CFCl\cdot + CF_3I \longrightarrow CF_3\cdot CF_2\cdot CFClI + CF_3\cdot \longrightarrow$ etc.

the propagation step to give $CF_3\cdot[CF_2\cdot CFCl]_n\cdot I$ competes with the chain-transfer step which gives the compound where $n = 1$. Since collision with a trifluoroiodomethane molecule is necessary to cause chain transfer, it is to be expected that a high

$CF_3I : C_2ClF_3$ ratio will favour formation of (I), and a low ratio polymer formation. This is true for any addition–polymerisation reaction of the type given above, but the ease of polymerisation of the olefin, also a major factor, often prevents control of the products being achieved merely by changing the ratio of the reactants. With chlorotrifluoroethylene and trifluoroiodomethane, however, appreciable control is possible in this way. When $CF_3I : C_2ClF_3$ is $>5 : 1$, only (I; $n = 1$) (85—90%) and (XI; $n = 2$) (10—15%) are formed, but as the ratio is decreased (*e.g.*, 1 : 1), compounds where $n > 1$ (*e.g.*, $n = 1$—5) are obtained; a moderate excess of chlorotrifluoroethylene (1 : 2) gives products with $n > 12$, and with a high $C_2ClF_3 : CF_3I$ ratio, a Kel-F type solid polymer is produced (see Table 3). In the compound (I; $n = 1$), the carbon–iodine bond is readily broken homolytically by ultra-violet light, and yields a $CF_3{\cdot}CF_2{\cdot}CFCl{\cdot}$ radical which, although less reactive than a $-CF_2{\cdot}$ radical, can initiate a chain reaction with chlorotrifluoroethylene. To obtain high yields of (I), therefore, the reaction products must be removed from the reaction zone and shielded from light.

Since a quantitative yield of (I) cannot be obtained even with a large excess of trifluoroiodomethane, it becomes essential to determine the constitution of the compounds where $n = 2$, 3, 4, etc., since it could be argued that if the $CF_3{\cdot}$ radical attacked the CFCl group of chlorotrifluoroethylene and gave $CF_3{\cdot}CFCl{\cdot}CF_2{\cdot}$, then this radical, being more reactive than the $CF_3{\cdot}CF_2{\cdot}CFCl{\cdot}$ radical, would combine with a second molecule of chlorotrifluoroethylene at a much greater rate. This could mean that the compound where $n = 1$ was $CF_3{\cdot}CF_2{\cdot}CFCII$, whereas the compounds where $n = 2$, 3, 4, etc., were $CF_3{\cdot}CFCl{\cdot}CF_2{\cdot}[C_2ClF_3]_{n-1}{\cdot}I$ or mixtures containing compounds having this general formula. Such a possibility would not alter the conclusion that the main attack of the $CF_3{\cdot}$ radical was on the CF_2 group of chlorotrifluoroethylene, but it would invalidate the statement that attack was exclusively on this group.

The compounds where $n > 1$ isolated from the reaction of trifluoroiodomethane with chlorotrifluoroethylene have been separated. That where $n = 2$ could have four possible formulæ (XI—XIV). The ultra-violet spectrum (Table 2) provides strong evidence that the CFCII chromophore is present, since the CF_2I chromophore is characterised by $\lambda_{max.}$ 250—251 mμ, whereas the CFCII chromophore has $\lambda_{max.}$ 261—262 mμ. Marked similarities can also be observed in the infra-red spectra of the compounds where $n = 1$ and 2. The compound where $n = 1$ has been proved to be (I); photochemical reaction of (I) with

TABLE 2. *Absorption spectra in ethanol.*

	$\lambda_{max.}$	ε	$\lambda_{min.}$	ε		$\lambda_{max.}$	ε	$\lambda_{min.}$	ε
$CF_3{\cdot}CF_2{\cdot}CFCII$ ...	262	315	235	240	$CF_3{\cdot}[CF_2{\cdot}CFCl]_5{\cdot}I$	Infl. 250—270	450	—	—
$CF_3{\cdot}[CF_2{\cdot}CFCl]_2{\cdot}I$	267·5	400	238·5	230					
$CF_3{\cdot}[CF_2{\cdot}CFCl]_3{\cdot}I$	268	450	245	380	$CF_2Cl{\cdot}CFCII$ [1] ...	261	295	233	195
$CF_3{\cdot}[CF_2{\cdot}CFCl]_4{\cdot}I$	262	470	250	420	$CF_2Cl{\cdot}CF_2I$ [2]	251·5	280	225·5	185
					$CF_3{\cdot}CF_2{\cdot}CF_2I$ [3] ...	250·5	230	225·5	150

[1] Haszeldine, *J.*, 1952, 4423. [2] *Nature*, 1950, **166**, 192. [3] *J.*, 1952, 3423.

chlorotrifluoroethylene yields compounds $CF_3{\cdot}CF_2{\cdot}CFCl{\cdot}[C_2ClF_3]_m{\cdot}I$; in the liquid phase, with a high ratio (I) : C_2ClF_3, the compound where $m = 1$ can be isolated in *ca.* 50% yield.

$$CF_3{\cdot}CF_2{\cdot}CFCl{\cdot} \xrightarrow{C_2ClF_3} CF_3{\cdot}CF_2{\cdot}CFCl{\cdot}[C_2ClF_3]_m{\cdot} \xrightarrow{CF_3{\cdot}CF_2{\cdot}CFCII} CF_3{\cdot}CF_2{\cdot}CFCl{\cdot}[C_2ClF_3]_m{\cdot}I$$

Infra-red spectroscopic examination shows that the compounds where $m = 1$, 2, or 3 are identical with the compounds where $n = 2$ (C.S. 44), 3, or 4 derived from trifluoroiodomethane and chlorotrifluoroethylene. Since the compound with $m = 1$ (*i.e.*, $n = 2$) derived from (I) can be only (XI) or (XII), depending on the direction of addition to chlorotrifluoroethylene, the possible formulæ (XIII) and (XIV) can be discarded.

(XI) $CF_3{\cdot}CF_2{\cdot}CFCl{\cdot}CF_2{\cdot}CFCII$ $\qquad$ $CF_3{\cdot}CF_2{\cdot}CFCl{\cdot}CFCl{\cdot}CF_2I$ (XII)

(XIII) $CF_3{\cdot}CFCl{\cdot}CF_2{\cdot}CF_2{\cdot}CFCII$ $\qquad$ $CF_3{\cdot}CFCl{\cdot}CF_2{\cdot}CFCl{\cdot}CF_2I$ (XIV; C.S. 46)

Now treatment of the compound where $n = 2$ with chlorine yields a trichloride, *A*, which must be (XV) or (XVI). The latter, which contains chlorine on adjacent carbon atoms, would yield a perhalogeno-olefin on treatment with zinc and ethanol, just as (IV)

readily gives hexafluoropropene. Reaction of the trichloride, *A*, with zinc and ethanol yields an olefin C_5HClF_8, whose infra-red spectrum reveals a vinylic carbon–hydrogen bond, and two bands in the C=C stretching vibration region, at 5·56 and 5·78 μ, closely

(XV; C.S. 45) $CF_3{\cdot}CF_2{\cdot}CFCl{\cdot}CF_2{\cdot}CFCl_2$ $CF_3{\cdot}CF_2{\cdot}CFCl{\cdot}CFCl{\cdot}CF_2Cl$ (XVI)
(XVII) $CF_3{\cdot}CF_2{\cdot}CFCl{\cdot}CF_2{\cdot}CHFCl$ $CF_3{\cdot}CF_2{\cdot}CFCl{\cdot}CF{:}CHF$ (XVIII; C.S. 46)

similar to those of 1 : 2 : 3 : 3 : 3-pentafluoropropene (IX). The absence of perhalogenoolefin thus eliminates (XVI), and as in the reaction of 1 : 1-dichlorohexafluoropropane with zinc and ethanol discussed earlier, the olefin C_5HClF_8 is clearly derived from (XV) by reduction of the $CFCl_2$ group to CHFCl—this gives (XVII), small amounts of which were isolated—followed by removal of fluorine and chlorine from adjacent carbon atoms to give $\cdot CF{:}CHF$, as in XVIII.

The 1 : 2-addition product of trifluoroiodomethane and chlorotrifluoroethylene is thus (XI).

The ultra-violet spectra of the compounds where $n = 3$, 4, or 5 (Table 2) are very similar to that of the compound where $n = 2$, and reveal the presence of the CFClI chromophore. As the chain length increases, so the minimum moves to longer wave-length, and the maximum to longer and then to somewhat shorter wave-length. When $n = 5$, the absorption of the CFClI chromophore is submerged in the general absorption of the $[CF_2{\cdot}CFCl]_n$ chain, and only an inflection is apparent. The infra-red spectra of compounds where $n = 3$—6 are also very similar and show that each contains $[CF_2{\cdot}CFCl{\cdot}CF_2{\cdot}CFCl]_x$ groups.

The results thus show that free-radical attack on chlorotrifluoroethylene is exclusively on the CF_2 group. It follows that polychlorotrifluoroethylene (" Kel-F ") is formed by head-to-tail addition, $nCF_2{:}CFCl \xrightarrow{R\cdot} R{\cdot}[CF_2{\cdot}CFCl]_x \cdots$, after initiation by a radical R·.

Henne and Kraus (*J. Amer. Chem. Soc.*, 1951, **73**, 1791) have reported that chlorotrifluoroethylene with bromotrichloromethane or trifluoroiodomethane yields $CCl_3{\cdot}CFCl{\cdot}CF_2Br$ or $CF_3{\cdot}CFCl{\cdot}CF_2I$ (II) respectively. Our results contradict this. Henne and Kraus argued that the trifluoroiodomethane addition product was (II), since on treatment with zinc and ethanol a gas of b. p. −28° was isolated without liberation of fluoride ion; the gas combined with chlorine to give a compound, b. p. 35°, n_D^{20} 1·3041, with properties said to agree with those of (IV). The pure 1 : 1-addition compound was, however, not isolated and there was no proof that (I) was not formed during reaction. The conditions used by these authors would favour polymerisation, but it now seems probable that the 1 : 1-addition product obtained in low yield was actually (I), and that the compound considered to be hexafluoropropene (b. p. −28°) was in fact 1 : 2 : 3 : 3 : 3-pentafluoropropene (b. p. −18·5°) obtained by reduction of (I) to (V) and dehalogenation, and that the dichloride was (VII) and not (IV).

The evidence for the bromotrichloromethane reaction product rested upon the following sequence (Henne and Kraus, *loc. cit.*):

$$C_3BrCl_4F_3\ (CCl_3{\cdot}CFCl{\cdot}CF_2Br) \xrightarrow[100°]{SbF_3Cl_2} C_3Cl_3F_5\ (CF_3{\cdot}CFCl{\cdot}CFCl_2) \xrightarrow[150°]{SbF_3Cl_2} C_3Cl_2F_6\ (CF_3{\cdot}CFCl{\cdot}CF_2Cl)$$

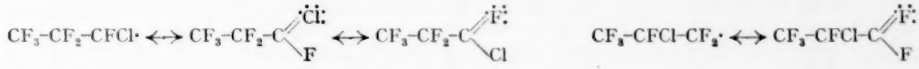
Treatment of the final product $C_3Cl_2F_6$ with zinc and ethanol gave a gas, b. p. −29°, considered to be hexafluoropropene. However, it has recently been shown (Haszeldine, *J.*, 1953, 922) that $CF_3\cdot$ and $CCl_3\cdot$ radicals behave similarly in addition reactions, and it is thus probable that the bromotrichloromethane addition product is $CCl_3{\cdot}CF_2{\cdot}CFClBr$, and that rearrangement has taken place during treatment with antimony trifluoride. Dr. W. T. Miller has stated (personal communication) that re-investigation of the bromotrichloromethane reaction reveals that the product is $CCl_3{\cdot}CF_2{\cdot}CFClBr$. All apparent differences between trifluoroiodomethane and bromotrichloromethane are thus removed. Further, the photochemical reaction of hydrogen bromide with chlorotrifluoroethylene has shown that the bromine atom, like the $CF_3\cdot$ and the $CCl_3\cdot$ radical, becomes attached to the CF_2 group (B. R. Steele, unpublished results).

In addition reactions involving ionic intermediates the negative substituent becomes attached to the CF_2 group of chlorotrifluoroethylene, indicating a polarisation $\overset{\delta+}{C}F_2{:}\overset{\delta-}{C}FCl$

(*e.g.*, iodine halides; Haszeldine, *J.*, **1952**, **4423**; alcohols and amines, Hanford and Rigby, U.S.P. 2,409,274/1946; Miller, Fager, and Griswold, *J. Amer. Chem. Soc.*, **1948**, **70**, 431; Young and Tarrant, *ibid.*, **1949**, **71**, 2432; Pruett *et al.*, *ibid.*, **1950**, **72**, 3646). One would thus predict that addition of a polyhalide CX_3Y in presence of aluminium chloride would yield $CX_3{\cdot}CFCl{\cdot}CF_2Y$ ($CX_3Y \xrightarrow{AlCl_3} [CX_3]^+[AlCl_3Y]^- \xrightarrow{CF_2{:}CFCl} [CX_3{\cdot}CFCl{\cdot}CF_2]^+ \longrightarrow CX_3{\cdot}CFCl{\cdot}CF_2Y$), and the earlier report (Coffman, Cramer, and Rigby, *ibid.*, 1949, **71**, 979) indicating the reverse addition with carbon tetrachloride has recently been corrected by Henne and Kraus (*ibid.*, 1951, **73**, 5303) (*i.e.*, $CCl_4 \longrightarrow CCl_3{\cdot}CFCl{\cdot}CF_2Cl$). Thus, addition of CX_3Y under conditions favouring radical intermediates gives an orientation different from that observed with ionic intermediates, and suggests that the $CX_3{\cdot}$ radical should not be regarded as an electrophilic reagent (cf. Part I, *J.*, 1952, 2504).

As observed with a series of olefins $R{\cdot}CH{:}CH_2$ (Part II, *loc. cit.*), attack of the $CF_3{\cdot}$ radical is on the carbon atom most open to attack for steric reasons. In fact, all radical addition reactions so far encountered could be explained on this simple concept. Until further evidence becomes available, however, this is accepted only with reserve, since it is difficult to explain the marked specificity of attack on olefins such as vinyl fluoride (Part II, *loc. cit.*) on purely steric grounds.

For attack of a $CF_3{\cdot}$ radical on chlorotrifluoroethylene, formation of the strong $CF_3{-}CF_2$ bond, as found in fluorocarbons, might be favoured over the (presumably) weaker $CF_3{-}CFCl$ bond, thereby favouring the formation of the intermediate $CF_3{\cdot}CF_2{\cdot}CFCl{\cdot}$ radical rather than the $CF_3{\cdot}CFCl{\cdot}CF_2{\cdot}$ radical. Other factors can, however, influence radical stability, *e.g.*, the relative contributions of resonance structures of the type



A full discussion of such factors is deferred.

Experimental

Trifluoroiodomethane was prepared from silver trifluoroacetate (Haszeldine, *J.*, 1951, 584) and was purified by distillation *in vacuo* (Found: *M*, 196. Calc. for CF_3I: *M*, 196). Chlorotrifluoroethylene was a commercial specimen, purified by repeated distillation *in vacuo*, and shown by its infra-red spectrum to be pure (Found: *M*, 116·5. Calc. for C_2ClF_3: *M*, 116·5).

Irradiations were carried out in sealed Pyrex (300 ml.) or silica (50 ml.) tubes, with extreme precautions to remove air, moisture, etc., which might inhibit or promote peroxide-catalysed or ionic reactions. Other reactions were in 30-ml. Pyrex tubes. A Hanovia lamp without the Wood's filter was the source of ultra-violet radiation.

Distillations were made in an apparatus, which will be described later, designed to reduce handling losses to a minimum.

Interaction of Trifluoroiodomethane and Chlorotrifluoroethylene.—(a) ***In silica vessels with a molar ratio ca. 5 : 1.*** Trifluoroiodomethane (15·4 g., 0·079 mole) and chlorotrifluoroethylene (2·0 g., 0·017 mole) were sealed *in vacuo* and irradiated at a distance of 8 cm., the liquid phase being shielded. Reaction in the vapour phase gave colourless liquids, which collected in the shielded portion of the tube. After 4 days, fractionation in a vacuum gave unchanged trifluoroiodomethane (12·4 g., 80%) (Found: *M*, 196), and a more volatile fraction (0·15 g.) which passed through a trap cooled to −140° and condensed in a trap at −183°. Spectroscopic examination of the latter fraction showed it to be a mixture of hexafluoroethane and chlorotrifluoromethane (approx. 1 : 1). The last two compounds were isolated only when irradiation was prolonged and trifluoroiodomethane was in excess, and involve radical combination and abstraction of chlorine from the polymer. The liquid products (4·8 g.) were distilled, to give 1-*chlorohexafluoro*-1-*iodopropane* (4·0 g., 84% based on trifluoroiodomethane used, 75% based on chlorotrifluoroethylene), b. p. 58°/330 mm., n_D^{20} 1·381 (Found: C, 11·4. C_3ClF_6I requires C, 11·5%), and 1 : 3-*dichlorononafluoro*-1-*iodopentane* (0·6 g., 9% based on trifluoroiodomethane used), b. p. 68°/32 mm., n_D^{20} 1·400 (Found: C, 13·8. $C_5Cl_2F_9I$ requires C, 13·9%). The reactions of this compound are described below. Only traces of material of higher molecular weight remained.

(b) ***In silica vessels with a molar ratio ca. 1 : 1.*** Chlorotrifluoroethylene (8·6 g., 0·074 mole) and trifluoroiodomethane (18·4 g., 0·094 mole), irradiated as in (a), gave unchanged trifluoro-

iodomethane (8·7 g., 47%) and liquid products faintly coloured with iodine. Distillation gave 1-chlorohexafluoro-1-iodopropane (9·8 g.), b. p. 60°/340 mm., n_D^{20} 1·381, 1 : 3-dichlorononafluoro-1-iodopentane (4·5 g.), b. p. 72°/34 mm., n_D^{20} 1·400, and a residue (3·0 g.) [shown later by combination with similar material to contain 1 : 3 : 5-*trichlorododecafluoro*-1-*iodoheptane* (*ca.* 1·5 g.), b. p. 74—6°/14 mm., n_D^{20} 1·402 (Found: C, 14·8. $C_7Cl_3F_{12}I$ requires C, 15·4%)], 1 : 3 : 5 : 7-*tetrachloropentadecafluoro*-1-*iodononane* (*ca.* 0·9 g.), b. p. 110°/9 mm., n_D^{20} 1·405 (Found: C, 16·2. $C_9Cl_4F_{15}I$ requires C, 16·3%), and a residual fraction, 1 : 3 : 5 : 7 : 9-*pentachloro-octadecafluoro*-1-*iodoundecane* (*ca.* 0·5 g.) (Found: C, 16·8. $C_{11}Cl_5F_{18}I$ requires 16·9%).

The compounds $CF_3{\cdot}[C_2ClF_3]_n{\cdot}I$ are readily decomposed by light or on contact with oxygen, yielding iodine and solid products; they must be stored in sealed containers in the dark.

(c) *In silica vessels, with an excess of chlorotrifluoroethylene.* Chlorotrifluoroethylene (6·1 g., 0·052 mole) and trifluoroiodomethane (6·1 g., 0·027 mole), irradiated as in (a), gave unchanged trifluoroiodomethane (1·1 g., 18%) (distilled in a vacuum system), liquids (10·5 g.), which on distillation through a short column gave fractions with b. p.s identical with those obtained as in (b) (n = 1—5: 4·0, 2·2, 1·4, 0·5, and 0·3 g. respectively), and a glass-like residue (1·3 g.) containing an average of eleven units of chlorotrifluoroethylene (Found: C, 18·9. Calc. for $C_{23}Cl_{11}F_{36}I$: C, 18·7%).

The yields of the compounds $CF_3{\cdot}[C_2ClF_3]_n{\cdot}I$ in experiments (a), (b), and (c) are shown in Table 3, and their ultra-violet spectra in Table 2.

TABLE 3.

	Yield (%) based on $CF_2{:}CFCl$			Yield (%) based on CF_3I		
n	(a)	(b)	(c)	(a)	(b)	(c)
1	75	44	25	84	63	50
2	16	29	20	9	21	20
3	—	11	15	—	5	10
4	—	7	6	—	4	4
5	—	4	3	—	1	2
Res.	—	—	20	—	—	3

(d) *In Pyrex vessels.* Trifluoroiodomethane (14·5 g., 0·075 mole) and chlorotrifluoroethylene (7·3 g., 0·063 mole) were sealed in a Pyrex tube, and the vapour phase was irradiated at a distance of 8 cm. for 7 days, the liquid phase being shielded. A small amount of solid polymer was formed on the side of the tube nearest the lamp. The unchanged reactants (15·3 g., 70%) (Found: *M*, 170) were distilled in a vacuum, and the liquid products (4·7 g.) yielded 1-chlorohexafluoro-1-iodopropane (3·0 g., 45% based on trifluoroiodomethane used), b. p. 67°/500 mm., 1 : 3-dichlorononafluoro-1-iodopentane (0·7 g., 14%), b. p. 46°/10 mm., n_D^{20} 1·400 [shown by their infra-red spectra to be identical with the fractions obtained as in (a) above], and material of higher b. p. (0·4 g.).

Chlorination of 1-*Chlorohexafluoro*-1-*iodopropane.*—The compound (3·3 g.) was sealed in a Pyrex tube with an excess of chlorine (1·29 g.) and exposed to ultra-violet light for 2 days. Mercury was then added to remove the chlorine and iodine chlorides, the volatile products were transferred to a vacuum system, and distillation gave 1 : 1-dichlorohexafluoropropane (1·74 g., 75%), b. p. 35° (Found: *M*, 222. Calc. for $C_3Cl_2F_6$: *M*, 221). Henne and Waalkes (*J. Amer. Chem. Soc.*, 1945, **67**, 1639) report b. p. 35°.

For comparison 1 : 2-dichlorohexafluoropropane was prepared in 90% yield by reaction of chlorine (0·55 g.) with hexafluoropropene (0·80 g.) in a Pyrex tube exposed to light, followed by treatment with mercury and fractionation *in vacuo* (Found: *M*, 222). The 1 : 2-dichloro-compound has a characteristic absorption band at 11·75 μ which is absent from the spectrum of 1 : 1-dichlorohexafluoropropane.

Conversion of 1-*Chlorohexafluoro*-1-*iodopropane into* 1-*Chloroheptafluoropropane.*—Dropwise addition of an excess of bromine trifluoride to 1-chlorohexafluoro-1-iodopropane (1·05 g.), contained in a platinum crucible fitting inside a Pyrex flask which was cooled to *ca.* −80°, gave volatile products collected in a trap cooled by liquid nitrogen. These were washed with 30% aqueous sodium hydroxide to remove traces of bromine and silicon tetrafluoride, and were distilled *in vacuo*, giving 1-chloroheptafluoropropane (0·52 g., 75%) (Found: *M*, 202. Calc. for C_3ClF_7: *M*, 204·5).

An authentic specimen of 1-chloroheptafluoropropane (b. p. −1°) was prepared by interaction of silver heptafluorobutyrate (2·0 g.) and an excess of chlorine at 100° for 12 hours. The gas was washed with 30% aqueous sodium hydroxide, and distilled, to give 1-chloroheptafluoropropane (1·01 g., 79%) (Found: *M*, 206).

Preparation of Perfluorohex-3-*ene from* 1-*Chlorohexafluoro*-1-*iodopropane.*—(a) *By photo-*

chemical reaction with mercury, etc. The compound (4·0 g.), sealed and vigorously shaken with mercury (11 g.) in a silica tube for 7 days with exposure to ultra-violet light, gave **3 : 4-*dichlorododecafluorohexane*** (1·60 g., 68%), b. p. 110—112°, n_D^{20} 1·324 (Found: C, 18·7. $C_6Cl_2F_{12}$ requires C, 19·4%). This (0·80 g.) was heated in a Carius tube with zinc dust (5 g.) and alcohol (10 ml.) at 110° for 24 hours, to give a volatile product which was washed with water and distilled, yielding ***perfluorohex*-3-*ene*** (0·37 g., 58%), b. p. 49° (Found: C, 24·3; *M*, 300. C_6F_{12} requires C, 24·0%; *M*, 300).

(b) *By reaction with zinc and dioxan.* The chlorofluoroiodopropane (2·0 g.) was sealed with zinc dust (5 g.) and dioxan (5 ml.), shaken vigorously, and slowly heated during 48 hours to 110°. The volatile products were washed with water, dried, and distilled in a vacuum, giving perfluorohex-3-ene (0·52 g., 54%) and 1-chloro-1 : 2 : 2 : 3 : 3 : 3-hexafluoropropane (0·13 g., 11%). Infra-red spectroscopic examination showed that the former was identical with the material obtained in (a) above, and the latter with the compound described below.

Reaction of **1-*Chlorohexafluoro*-1-*iodopropane* with Zinc and Ethanol.**—A solution of the iodo-compound (4·7 g.) in ethanol (10 ml.) was slowly added to a well-stirred mixture of zinc dust (50 g.) and refluxing ethanol (100 ml.) to give, by a slow reaction requiring 40 hr. for completion, volatile products passing through the reflux water-condenser. These were washed with water and distilled *in vacuo*, to give a fraction (1·90 g.) condensing at −95°, shown by infra-red spectroscopic examination to be 1-chloro-1 : 2 : 2 : 3 : 3 : 3-hexafluoropropane contaminated by olefinic compounds. The material was sealed with an excess of chlorine (0·7 g.) for 2 days and redistilled, to give pure **1-*chloro*-1 : 2 : 2 : 3 : 3 : 3-*hexafluoropropane*** (1·70 g., 60%), b. p. 20° (Found: C, 19·4; H, 0·3%; *M*, 187. C_3HClF_6 requires C, 19·4; H, 0·5%; *M*, 186·5), and two dichlorides; the first dichloride (0·24 g.), on fractionation in a micro-distillation apparatus, gave **3 : 4-dichlorododecafluorohexane** (*ca.* 9%), b. p. 110°, n_D^{20} 1·323, identical with the material obtained earlier; the second (*ca.* 0·1 g.) was shown to be **1 : 2-dichloro-1 : 2 : 3 : 3 : 3-pentafluoropropane** (see below). Infra-red spectroscopic examination showed that hexafluoropropene was not present in the olefinic compounds mentioned above (see also **1 : 2 : 3 : 3 : 3-pentafluoropropene**, below)

Reaction of Dichlorohexafluoropropanes with Zinc and Ethanol.—Zinc dust (4 g.), ethanol (8 ml.), and **1 : 1-dichlorohexafluoropropane** (1·37 g.) were sealed together and stirred at 50° for 16 hr. The volatile products were then washed with water, dried (phosphoric anhydride), and distilled *in vacuo*, to give **1-chloro-1 : 2 : 2 : 3 : 3 : 3-hexafluoropropane** (0·937 g., 80%) (Found: *M*, 185. Calc. for C_3HClF_6: *M*, 186·5) (identified tensimetrically and by its infra-red spectrum) and **1 : 2 : 3 : 3 : 3-pentafluoropropene** (0·10 g., 12%) (Found: *M*, 131), b. p. −18·5° (shown to be identical with the material described below by comparison of infra-red spectra).

Similar treatment of **1 : 2-dichlorohexafluoropropane** (0·95 g.) at 40° for 18 hr. gave **hexafluoropropene** (0·58 g., 90%) (Found: *M*, 149. Calc. for C_3F_6: *M*, 150), identified tensimetrically.

Preparation of **1 : 2 : 3 : 3 : 3-*Pentafluoropropene*.**—1-Chloro-**1 : 2 : 2 : 3 : 3 : 3-hexafluoropropane** (0·644 g.), heated and shaken at 120° for 7 days with zinc dust (4 g.) and ethanol (10 ml.), gave **1 : 2 : 3 : 3 : 3-pentafluoropropene** (0·240 g., 53%), b. p. −18·5° (Found: C, 27·6%; *M*, 131·5. C_3HF_5 requires C, 27·3% *M*, 132); a small amount of hydrogen was formed during reaction.

The infra-red spectrum of the pentafluoropropene shows the vinylic C–H stretching vibration at 3·18 μ and the C=C stretching vibration at 5·74 μ; the weak band at 5·56 μ may be caused by *cis–trans*-isomerism. Hexafluoropropene has the strong C=C stretching absorption at 5·56 μ, but the strong doublet at 12·97—13·05 μ readily enables even small amounts of the olefin to be detected when mixed with **1 : 2 : 3 : 3 : 3-pentafluoropropene**.

Reaction of the pentafluoropropene with a slight excess of chlorine in a sealed tube gave **1 : 2-dichloro-1 : 2 : 3 : 3 : 3-pentafluoropropane** (80%), b. p. 56°, n_D^{16} 1·339.

Reaction of **1-*Chlorohexafluoro*-1-*iodopropane* with *Chlorotrifluoroethylene*.**—(a) ***With excess of* 1-*chlorohexafluoro*-1-*iodopropane*.** The iodo-compound (2·0 g., 0·0064 mole) was sealed in a 10-ml. silica tube with chlorotrifluoroethylene (0·277 g., 0·0024 mole) and the *liquid* phase was irradiated for 18 hr., the vapour phase being shielded. Fractionation gave unchanged chlorotrifluoroethylene (0·060 g., 22%) and a liquid coloured with iodine (cf. vapour-phase reaction where photolysis of reaction products is negligible). The liquid was shaken with sodium thiosulphate solution and distilled from phosphoric anhydride, to give unchanged **1-chlorohexafluoro-1-iodopropane** (1·0 g.), b. p. 58°/330 mm., **3 : 4-dichlorododecafluorohexane** (0·2 g.), b. p. 50°/200 mm. (formed by dimerisation of $CF_3{\cdot}CF_2{\cdot}CFCl{\cdot}$ radicals), **1 : 3-dichlorononafluoro-1-iodopentane** (0·4 g., 50% based on C_2ClF_3 used), b. p. 70°/34 mm., and material

(0·2 g.) of higher b. p. Infra-red spectroscopic examination showed that these fractions were identical with the materials obtained as above.

(b) *With an excess of chlorotrifluoroethylene.* The iodo-compound (2·0 g., 0·0064 mole) and chlorotrifluoroethylene (1·4 g., 0·012 mole) were exposed to ultra-violet light, as in (a), for 4 days, giving unchanged 1-chlorohexafluoro-1-iodopropane (0·5 g.), 1 : 3-dichlorononafluoro-1-iodopentane (0·4 g., 8% based on C_2ClF_3), b. p. 78°/37 mm., 1 : 3 : 5-trichlorododecafluoro-1-iodoheptane (*ca.* 0·5 g., 15% based on C_2ClF_3), b. p. 72°/17 mm., 1 : 3 : 5 : 7-tetrachloropentadecafluoro-1-iodononane (*ca.* 0·7 g., 26% based on C_2ClF_3), b. p. 110°/10 mm., and 1 : 3 : 5 : 7 : 9-pentachloro-octadecafluoro-1-iodoundecane (*ca.* 1·0 g., 43% based on C_2ClF_3). These fractions were shown by their infra-red spectra to be identical with materials obtained from trifluoroiodomethane and chlorotrifluoroethylene.

Reaction of 1 : 3-*Dichlorononafluoro*-1-*iodopentane with Zinc and Ethanol.*—The compound (1·79 g.) was stirred with zinc dust (4 g.) and ethanol (15 ml.) for 4 hr. at 0—4°. Filtration followed by addition of water gave a lower layer, b. p. <120°, which was shaken with mercury and exposed to ultra-violet light to remove unchanged iodo-compound. Distillation then gave 1 : 3-dichloro-1 : 2 : 2 : 3 : 4 : 4 : 5 : 5 : 5-nonafluoropentane, b. p. 103° (micro), n_D^{20} 1·334 (Found : C, 20·7. $C_5HCl_2F_9$ requires C, 19·8%), shown by its infra-red spectrum and analysis to be slightly contaminated with the chloro-octafluoropentene. The infra-red spectrum showed bands at 3·38 and 3·5 μ (C–H stretching) 7·50, 8·06, 8·25, 8·68 (w), 8·85 (w), 9·08 (w), 9·40 (w), 9·65 (w), 10·50, 11·45, 12·57, 13·15 (w), 13·23, 14·04, 14·65 and 15·32 μ.

Preparation of 1 : 1 : 3-*Trichlorononafluoropentane and its Reaction with Zinc and Ethanol.*—1 : 3-Dichlorononafluoro-1-iodopentane (2·0 g.) was sealed in a small Pyrex tube with chlorine (0·35 g.), and exposed to ultra-violet light for 2 days, and then shaken with mercury. Distillation gave 1 : 1 : 3-*trichlorononafluoropentane* (1·10 g., 70%), b. p. 119°, n_D^{20} 1·345 (Found : C, 17·6. $C_5Cl_3F_9$ requires C, 17·8%).

The trichloride (0·66 g.) was sealed with zinc dust (2 g.) and ethanol (10 ml.) and stirred at 110° for 24 hr., to give, after filtration and precipitation of the organic phase by addition of an excess of water, 3-*chloro*-1 : 2 : 3 : 4 : 4 : 5 : 5 : 5-*octafluoropent*-1-*ene* (0·24 g., 50%), b. p. 67°, n_D^{20} 1·306 (Found : C, 24·6; H, 0·7%; *M*, 245. $C_5Cl_2F_8$ requires C, 24·2; H, 0·4%; *M*, 248·5), and a compound of higher b. p., probably 1 : 3-dichloro-1 : 2 : 2 : 3 : 4 : 4 : 5 : 5 : 5-nonafluoropentane (0·07 g., 12%) (as obtained earlier from the 1 : 3-dichlorononafluoro-1-iodopentane).

Infra-red and Ultra-violet Spectra.—These were determined by use of a Perkin–Elmer Model 21 instrument with rock-salt optics, and of a Unicam Ultra-violet Spectrophotometer.

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322. *The Chromatography of Gases and Vapours. Part II.**

By D. H. JAMES and C. S. G. PHILLIPS.

An apparatus is described for the analysis and separation of mixtures of volatile substances by the use of chromatographic methods in which the moving phase is a gas. Results are quoted to illustrate the application of adsorption and partition techniques. Particular attention has been given to displacement (adsorption) analyses from charcoal columns at 100°, where an accuracy of better than 1% can be obtained.

DESPITE the wide interest in chromatographic methods, surprisingly little has been published in which the traditional moving-liquid phase has been replaced by a moving-gas phase. In part this may be ascribed to historical accident. Chromatography was first used for the more complex and therefore more feebly volatile molecules, and has since been largely employed only for those problems where other methods have failed. In many ways it would have been more logical had conventional chromatographic methods developed from gas chromatography rather than the reverse, for the behaviour of gases is simpler and better understood than that of liquids.

* Part I is considered to be the paper by Phillips in *Discuss. Faraday Soc.*, 1949, **7**, 241.

Most of the published work on gas chromatography has been concerned with the use of adsorption columns of charcoal or silica gel. Turner (*Oil Gas J.*, April 29th, 1943; *Petrol. Refiner*, May, 1943) described the fractional desorption of vapours from a charcoal column by means of a heater. Glueckauf (*Discuss. Faraday Soc.*, 1947, **7**, 199) obtained an enrichment of the neon isotopes on passing neon through charcoal at −196°. Turkel'taub (*J. Anal. Chem. U.R.S.S.*, 1950, **5**, 200) devised a technique in which hydrocarbons removed from a charcoal column were estimated by combustion. Cremer and Muller (*Mikrochem. Microchim. Acta*, 1951, **36/37**, 533) separated various acetylenes and olefins on columns of charcoal and silica gel. The curved isotherms typical of adsorption equilibria make the method particularly suitable for the application of the *displacement* technique, as was first demonstrated by the work of Claesson (*Arkiv Kemi, Min., Geol.*, 1946, *A*, **23**, No. 1), and later by Phillips (Part I, *loc. cit.*), and by Hammar (*Svensk Kem. Tidskr.*, 1951, **63**, 125). The potentialities of gas chromatography with partition columns, in which the static phase is a high-boiling liquid, has been well demonstrated by Martin and James's recent work (*Biochem. J.*, 1952, **50**, 679). The linear isotherms obtained in partition equilibria make partition columns suitable for the *elution* technique.

We believe that gas chromatographic methods deserve a much fuller investigation, because the more nearly ideal behaviour of gases should make it possible to effect separations with even greater efficiency in gas chromatography than has already been obtained in liquid chromatography. In particular, equilibria involving gases, especially between gases and surfaces, are set up much more rapidly than equilibria involving liquids, where " solvent cage " effects are present. An investigation of the use of gas-chromatographic methods has therefore been instituted, in which both the adsorption (displacement) and the partition (elution) technique are being employed side by side. Some of the general results obtained have already been reviewed (Griffiths, James, and Phillips, *Analyst*, 1952, **77**, 897). The present paper is largely concerned with the analyses and separations obtained with the displacement technique, and in particular with the use of charcoal columns operated at 100°. Some results obtained with the partition technique are also included. A later paper will describe the use of the chromatographic apparatus for the determination of adsorption isotherms.

Experimental

Apparatus.—The complete apparatus is represented by the block diagram (Fig. 1). The mixture to be separated is placed in one of the introductory tubes I_A or I_P, and carried on to

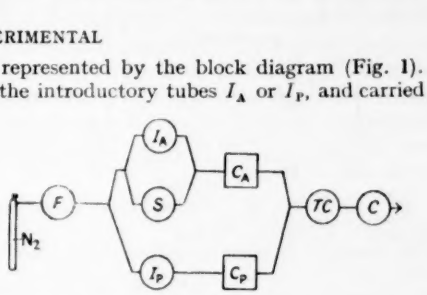


FIG. 1. *Block diagram of apparatus.*

the adsorption column C_A or the partition column C_P in a stream of nitrogen from the cylinder. For application of the elution technique a constant flow of nitrogen (solvent) is then passed through the column by operation of the flow-control *F*. For use of the displacement technique (with the adsorption column) the nitrogen stream is switched through the saturator *S*, by means of which a constant concentration of displacer vapour is introduced into the nitrogen. After leaving either column, the gas stream passes through the thermal conductivity cell (*TC*) and the fraction collector (*C*).

The flow-control *F* has been specially designed for gas chromatography and is described by us elsewhere (*J. Sci. Instr.*, 1952, **29**, 362).

The adsorption column C_A is illustrated in Fig. 2. It consists of three sections (see Part I), each 10 cm. long, the first of diameter 16 mm., the second 8 mm., and the final " sharpening " section 2 mm. The column is surrounded by a jacket, kept at a fixed temperature by vapour from a smooth-boiling electrically heated flask. The charcoal used for most of the work (Sutcliffe and Speakman, 208C) was of particle size B.S.S. 30—40 (0·014—0·020" diameter). It is dried at 140° before use.

The partition column C_P is illustrated in Fig. 3. It consists of a length of 3-mm. bore tubing about 75 cm. long. This column can also be jacketed when required. Silicone fluid (702), nitrobenzene, " tricresyl " phosphate, and dibutyl phthalate have been employed as column liquids. They are supported on a non-adsorbent material (Celite, Johns-Mansville). The Celite is freed from dust by sedimentation in water, dried at 100°, thoroughly mixed with about 30% by weight of the column liquid, and packed into the tube with vigorous agitation from an electric motor.

The saturator *S*, illustrated in Fig. 4, consists of a jacketed tube containing a sintered-glass

FIG. 2. *Adsorption column.* FIG. 3. *Partition column.* FIG. 4. *Saturator.*

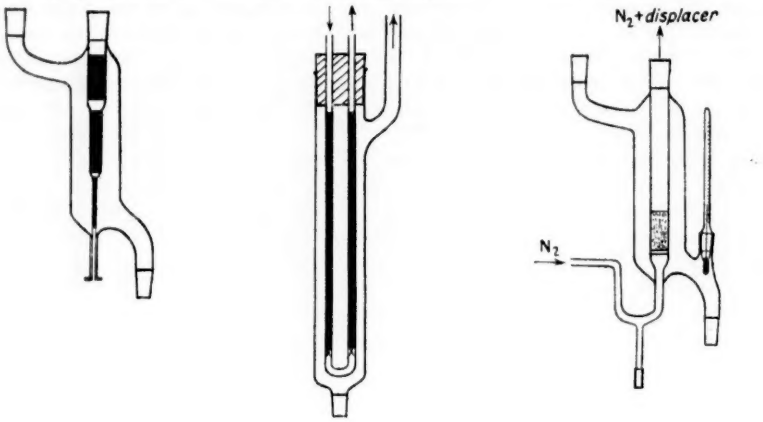


FIG. 5. FIG. 6.

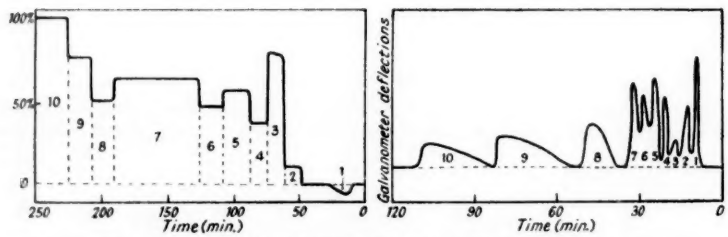


FIG. 5. *A typical displacement analysis (Analysis* O, *Table* 2).

Components of mixture : Water (1), *diethyl ether* (2), *chloroform* (3), *ethyl acetate* (4), *thiophen* (5), *dioxan* (6), *pyridine* (7), *butyl acetate* (8), *chlorobenzene* (9), *and bromobenzene* (10) *displacer.*

FIG. 6. *A typical partition analysis.*

Column : 1·5 ml. of dibutyl phthalate supported on " Celite." Temperature, 56°. *Flow rate,* 45 *ml. per min. Analysis of mixture consisting of 0·03 ml. each of* n-*pentane* (1), n-*hexane* (2), *siloxane* (DC 200/0·65 *cs.*) (3), cyclo*hexane* (4), *carbon tetrachloride* (5), *benzene* (6), *thiophen* (7), *toluene* (8), *pyridine* (9), *and* m-*xylene* (10).

disc (grade 2), through which the nitrogen passes as small bubbles into the liquid displacer. Despite its simple design, a close investigation has shown it to be extremely efficient.

The thermal-conductivity cell *TC* follows the design given in Part I (*loc. cit.*) and is also jacketed to prevent condensation. The cell wire forms one arm of a Wheatstone bridge, the other three arms consisting of manganin coils immersed in thermostat oil, at room temperature. The bridge is driven by a high-capacity 2-volt battery, and the out-of-balance voltage applied to a recording galvanometer (Ether Indicorder; Ether Ltd., Birmingham). The cell wire is of platinium, 14 cm. long and 0·05 mm. in diameter. It has a cold resistance of approx. 7 ohms. Under operating conditions, *i.e.*, with the jacket at 100°, and with nitrogen flowing through the cell, the resistance rises to 10·10 ohms, and the wire temperature is 127·7°. The temperature rises as vapours leave the column in the nitrogen stream, and is, for example, 128·7°

for the benzene step, and 130·0° for the bromobenzene (displacer) step. Various cell designs have been tried. All are somewhat sensitive to vibration, which leads to fluctuations on the recorder. These fluctuations are reduced to the order 0·0—0·5% of displacer step height by mounting the cell support on thick rubber. Typical results obtained on the recorder are illustrated in Fig. 5 (displacement), and Fig. 6 (elution from a partition column).

Tubes connecting saturator, column, and thermal-conductivity cell are kept at a high enough temperature to prevent condensation, by means of wire-wound heaters.

Results and Discussion.

The results obtained by the adsorption (displacement) technique are discussed below [Sections (i)—(viii)]. Some typical displacement analyses are given in Tables 1, 2, and 3. The results obtained with the partition (elution) technique are discussed in Section (ix).

(i) *Range of Technique.*—The type of substance, suitable for a particular displacement analysis, is largely governed by the sensitivity of the thermal-conductivity recorder, and

Table 1. *Estimation of benzene and toluene in various mixtures.*

Found	Correct	Other components of mixture	Found	Correct	Other components of mixture
	Benzene, % (by wt.)			Toluene, % (by wt.)	
99·5	100	—	100·5	100	—
100	100	—	100	100	—
50·7	51·4	PhMe	49·3	48·6	C_6H_6
49·0	49·7	PhMe	51·0	50·3	C_6H_6
41·6	41·8	PhCl	46·2	46·2	PhCl
46·6	46·8	C_5H_5N	45·7	46·2	o-$C_6H_4Me_2$
24·3	24·3	PhMe + PhCl	24·6	24·2	C_6H_6 + PhCl
20·3	20·2	PhMe + o-$C_6H_4Me_2$	38·2	38·0	C_6H_6 + o-$C_6H_4Me_2$
35·7	35·7	Et_2O + PhMe	35·4	35·2	Et_2O + C_6H_6

by the character of the displacing vapour. As a general rule the separations follow the order of boiling points fairly closely, a given vapour displacing the vapours of all other substances of lower b. p. [Exceptions on the charcoal employed include *n*-butyl alcohol (b. p. 117°) before pyridine (115°), thiophen (84°) before benzene (80°), pyridine (115°) before toluene (111°), *cyclo*hexane (81°) before benzene (80°), and siloxane (DC 200/1·5 cs.) (192°) before bromobenzene (156°).] The saturator temperature (and hence the concentration of displacer vapour in the nitrogen stream) is chosen so that the various substances leave the column at concentrations sufficient for the thermal-conductivity recorder to differentiate one step from the next. With our apparatus, a displacer concentration of about 7% (molar) in nitrogen is found to be convenient, and this has led, in most of our work, to the use of nitrogen saturated with ethyl acetate at 0° for columns at room temperature, and nitrogen saturated with bromobenzene at 77° for columns operated at 100°. This results in step concentrations of between 6 and 7 molar %. Low displacer concentrations give rise to longer steps and increased quantitative accuracy, but lowered qualitative distinction. The latter factor can, of course, be improved by altering the recording device, and by this means (see Griffiths, James, and Phillips, *loc. cit.*) we have even succeeded in using as displacer a stream of nitrogen saturated with ethyl benzoate (b. p. 213°) at 0°.

An individual step height on the recorder depends not only upon the position of the step in the displacement sequence (*i.e.*, upon b. p.), but also upon the sensitivity of the thermal-conductivity cell to the particular substance. This is illustrated in Fig. 7, where a number of typical step heights obtained with bromobenzene displacer are plotted against the corresponding b. p.s. It will be observed, for example, that chlorinated substances produce particularly large step heights.

Substances whose b. p.s lie considerably (*i.e.*, about 120—150°) below the b. p. of the displacer will not give satisfactory steps and tend to appear as elution peaks.

(ii) *Quantity required for an Analysis.*—The apparatus described will produce a clearly defined step for as little as 0·02 g. of a normal component such as benzene. Change of displacer will alter this value. Thus if the saturator is kept at 77°, *iso*amyl acetate (b. p. 139°) displacer will only give a well-defined step for 0·04 g. of benzene, while with *o*-dichlorobenzene (b. p. 179°) as displacer only 0·01 g. is required. Smaller quantities only give

TABLE 2. *Typical displacement analyses.*

Adsorbent : activated charcoal. Displacer : bromobenzene.
Flow-rate : 46·5 ml./min. Column temp. : 100°.

Analysis	Component	Step height (% of PhBr)	Wt., g. Found	Wt., g. Correct	Wt., % Found	Wt., % Correct
A	*cyclo*Hexane	36·0	0·0750	0·0740	48·2	47·9
	Pyridine	60·0	0·0805	0·0805	51·9	52·1
B	Ethyl acetate	36·5	0·1445	0·1460	50·0	50·4
	Butyl acetate	50·0	0·1445	0·1435	50·0	49·6
C	Methyl acetate	26·0	0·1410	0·1400	45·0	44·7
	Siloxane (D.C. 200/0·65 cs.)	34·0	0·1720	0·1725	55·0	55·3
D	Propyl acetate	46·0	0·1610	0·1595	52·6	52·3
	Butyl acetate	50·0	0·1445	0·1455	47·4	47·7
E	Pyridine	60·0	0·3940	0·3920	69·2	69·0
	Butyl acetate	50·0	0·1755	0·1760	30·8	31·0
F	*n*-Hexane	30·0	0·0405	0·0396	26·4	26·2
	n-Heptane	41·5	0·1130	0·1120	73·6	73·8
G	*cyclo*Hexane	36·0	0·0775	0·0775	18·2	18·3
	Pyridine	60·0	0·1690	0·1698	39·6	39·9
	Chlorobenzene	76·0	0·1810	0·1775	42·2	41·8
H	Benzene	44·5	0·0797	0·0793	20·3	20·2
	Toluene	55·0	0·1482	0·1492	38·2	38·0
	o-Xylene	61·5	0·1625	0·1640	41·5	41·8
I	Ethyl acetate	36·5	0·0882	0·0875	28·3	28·3
	Propyl acetate	46·0	0·0875	0·0865	28·2	27·9
	Butyl acetate	50·0	0·1360	0·1360	43·6	43·8
J	*n*-Pentane	16·0	0·1240	0·1250	31·7	31·9
	n-Hexane	30·0	0·1320	0·1320	33·5	33·5
	n-Heptane	41·5	0·1370	0·1360	34·8	34·6
K	*n*-Propyl chloride	24·0	0·1780	0·1780	17·9	18·3
	n-Pentane	16·0	0·1190	0·1210	11·9	12·4
	Ethyl acetate	36·5	0·1260	0·1800	12·6	18·4
	Carbon tetrachloride	75·0	0·3960	0·3200	39·6	32·8
	Propyl acetate	46·0	0·1800	0·1760	18·0	18·1
L	*cyclo*Hexane	36·0	0·0920	0·0935	9·1	9·0
	Benzene	44·5	0·1800	0·1760	17·7	17·0
	Toluene	55·0	0·1630	0·1730	16·2	16·7
	Pyridine	60·0	0·1880	0·1960	18·5	18·9
	Chlorobenzene	76·0	0·2200	0·2220	21·7	21·5
	o-Xylene	61·5	0·1700	0·1730	16·8	16·9
M	*n*-Pentane	16·0	0·1270	0·1260	11·5	11·4
	*cyclo*Hexane	36·0	0·1560	0·1560	14·1	14·0
	n-Hexane	30·0	0·0920	0·1320	8·4	11·8
	Benzene	44·5	0·2130	0·1760	19·3	15·9
	Pyridine	60·0	0·1760	0·1760	15·8	15·9
	o-Xylene	61·5	0·3420	0·3340	30·9	31·0
N	Water	no step	0·0820	0·0800	10·6	10·4
	*iso*Pentane	10·0	0·0160	0·0160	2·1	2·1
	n-Pentane	16·0	0·0838	0·0838	10·9	11·0
	n-Hexane	30·0	0·0746	0·0725	9·6	9·4
	Benzene	44·5	0·1330	0·1340	17·2	17·5
	n-Heptane	41·5	0·0980	0·0950	12·7	12·4
	Toluene	55·0	0·1313	0·1313	17·0	17·0
	Chlorobenzene	76·0	0·1540	0·1550	19·9	20·2
O	Water	no step	0·0430	0·0400	1·9	1·8
	Diethyl ether	12·0	0·0775	0·0785	3·4	3·5
	Chloroform	77·0	0·1920	0·1950	8·5	8·7
	Ethyl acetate	36·5	0·1155	0·1170	5·1	5·2
	Thiophen	55·0	0·2025	0·2070	9·1	9·3
	Dioxan	45·0	0·1650	0·1660	7·4	7·4
	Pyridine	61·0	1·0855	1·0800	48·5	48·3
	Butyl acetate	50·0	0·1830	0·1765	8·2	7·9
	Chlorobenzene	76·0	0·1755	0·1770	7·9	7·9

TABLE 3. *Displacement analyses with one component present as a small percentage.*

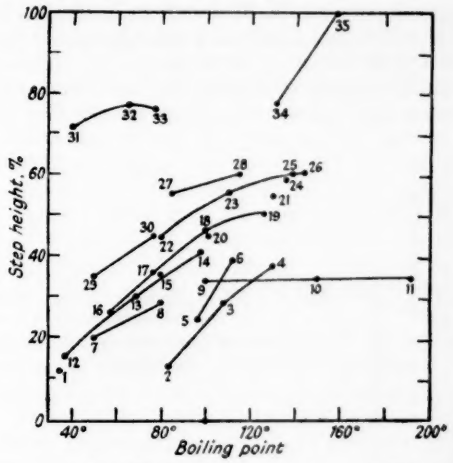
Conditions as in Table 2.

Analysis	Component	Step height (% of PhBr)	Wt., g. Found	Wt., g. Correct	Wt., % Found	Wt., % Correct
P	Benzene	44·5	0·0592	0·0588	1·68	1·66
	Toluene	55·0	3·47	3·47	98·3	98·3
Q	Benzene	44·5	3·54	3·52	98·1	98·2
	Toluene	55·0	0·0690	0·0695	1·94	1·75
R	Pentane	16·0	0·0207	0·0205	0·60	0·60
	Benzene	44·5	3·72	3·72	99·4	99·4

rise to points of inflexion, which, however, may still be used for quantitative and rough qualitative analysis. It is to be noted that the limit is an absolute one, and is independent of the amount of other components present in a mixture. This feature of the method makes it very suitable for the analysis of traces of one substance in relatively large amounts of another, as is shown by Analyses P, Q, and R in Table 3. Furthermore, small traces of a component will be concentrated in the column, so that the method is also very suitable for its isolation.

(iii) *Accuracy of Analyses.*—The accuracy of an analysis depends upon the accuracy with which a step length can be measured, and the accuracy with which various experimental parameters (such as flow-rate, saturator, and column temperatures) can be kept

FIG. 7. *Plot of step height (measured as % of displacer-bromobenzene-step height) against boiling point, for a number of compounds displaced from a charcoal column at* 100°.



1. Diethyl ether.
2. *iso*Propyl alcohol.
3. *iso*Butyl alcohol.
4. *iso*Amyl alcohol.
5. *n*-Propyl alcohol.
6. *n*-Butyl alcohol.
7. Acetone.
8. Ethyl methyl ketone.
9. Siloxane DC 200 0·65 cs.
10. ,, ,, 1·0 cs.
11. ,, ,, 1·5 cs.
12. *n*-Pentane.
13. *n*-Hexane.
14. *n*-Heptane.
15. *cyclo*Hexane.
16. Methyl acetate.
17. Ethyl acetate.
18. Propyl acetate.
19. Butyl acetate.
20. Dioxan.
21. *cyclo*Pentanone.
22. Benzene.
23. Toluene.
24. Ethylbenzene.
25. *m*- and *p*-Xylene.
26. *o*-Xylene.
27. Thiophen.
28. Pyridine.
29. *n*-Propyl chloride.
30. *n*-Butyl chloride.
31. Methylene dichloride.
32. Chloroform.
33. Carbon tetrachloride.
34. Chlorobenzene.
35. Bromobenzene.

constant. The latter tend to vary more from one run to another than they do during one run itself, so the relative values for the components of one mixture are often more accurate than the absolute accuracy with which each is measured. The step length measurement is essentially one of time and can be made with more precision than the measurement of step height, which depends upon the response of the thermal-conductivity cell. The method is therefore particularly suited for quantitative work. An accuracy of better than 1% is readily obtained as will be seen from the tables.

(iv) *Time required for an Analysis.*—The time taken for an analysis will depend upon the nitrogen flow-rate employed and the amount of material to be analysed. Throughout our work we have employed a constant flow-rate of 46·5 ml. of nitrogen per minute. A faster flow-rate reduces the accuracy somewhat, but there has been little improvement on reducing the flow-rate below this figure. An analysis of 0·1 g. takes about 20 min.' running time, and correspondingly with 1 g., 200 min. The actual manipulation time required is, of course, considerably less, for the recording equipment runs automatically.

The various operations required to change from one analysis to the next (change of charcoal, introduction of mixture to be analysed, and connection to the saturator) can be effected in under 10 min., and will be very nearly independent of the amount of sample.

(v) *Efficiency of Separations.*—It has been found in liquid chromatography that it is possible, as a result of complex adsorption isotherms, for sharp displacement steps to be produced, which nevertheless do not consist of pure components. The high accuracy of the gas-chromatographic analyses over wide variations of mixture composition suggests that this cannot be so in the case of gas chromatography. It seemed, however, essential to confirm this, and a number of separate checks have been made on samples isolated from individual steps by the fraction collector. Mixed steps were only found when it was attempted to separate benzene and *cyclo*hexane on the normal coarse charcoal, or in other instances when the column had been seriously overloaded. The separation of benzene and *cyclo*hexane proved to be quite satisfactory with finer charcoal [see (vii) below]. For an example of overloading, compare results M and N in Table 2. Analysis M was carried out with only 15 ml. of charcoal, and results in a poor separation of *n*-hexane and benzene. Analysis N, carried out with 25 ml. of charcoal, gave a good separation.

The checks on the purity of individual fractions have been made by measurements of liquid density and of b. p.s, and by running samples on partition columns. Liquid densities were determined by a micropyknometer capable of handling 0·02 ml. with an accuracy of 0·2%.

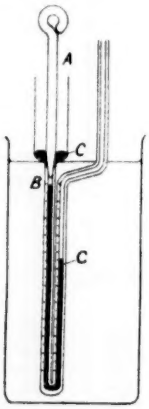


FIG. 8. *Micro-apparatus for determination of boiling points.*
A, Ground glass stopper. B, Sample. C, Mercury.

Boiling points were measured in a modified micro-Schleiermacher apparatus. It was found impossible to obtain accurate results with the recommended sealing-off technique, as a result of the trapping of small air bubbles and the presence of air in the mercury. This technique was replaced by the use of a ground-glass stopper (Fig. 8), which enables such bubbles of air to be removed with ease whenever they appear. With this simple modification it was then found possible to measure b. p.s on as little as 0·02 ml. of a liquid, with an accuracy of ±0·1°. A larger version of this apparatus, with essentially the same design, has been described by Simmons (*J. Chem. Educ.*, **1947**, **24**, 233).

TABLE 4. *Analysis of fractions from a displacement run.*

	B. p.		Density	
Step	Found	Correct	Found	Correct
Diethyl ether	34·5°	34·5°	0·709	0·714
Benzene	80·1	80·2	0·880	0·879
Toluene	110·9	110·8	0·864	0·866

Some typical results obtained for an ether, benzene, and toluene mixture are given in Table 4. Boiling-point data for ether–benzene and benzene–toluene systems (see I.C.T.) show that ether containing 1% of benzene would boil 0·25° higher, and benzene containing

1% of toluene would boil 0·23° higher. These results on the purity of individual steps were confirmed by partition experiments in which no small extra peaks could be discerned when each fraction was run separately.

(vi) *Recovery of Components.*—Small amounts of irreversible adsorption would lead to less than 100% recovery, although sharp steps could still be obtained, and accurate analyses performed under constant conditions. It is, however, found that the step length is independent of the amount of charcoal employed. The 100% recovery has been further confirmed by comparison with careful vapour pressure–step height measurements undertaken in connection with the isotherm determinations (James and Phillips, unpublished). The foregoing remarks do not hold good for the adsorption of aldehydes and acids on charcoal, or for the adsorption of olefins on silica gel, where irreversible adsorption appears to take place.

(vii) *Separation of Close-boiling Mixtures.*—The efficiency of the gas-chromatographic technique is well illustrated by the ease with which many close-boiling mixtures are separated. The following mixtures have been readily separated by the normal technique: (*a*) *n*-butyl alcohol (b. p. 117°) and pyridine (115°), (*b*) *iso*butyl alcohol (108°) and toluene (111°), (*c*) water (100°) and dioxan (101°) (see Fig. 5), and (*d*) ethyl acetate (77·2°) and carbon tetrachloride (77·5°). Such mixtures are naturally somewhat more difficult than those containing only substances of very different boiling points. Analysis K (Table 2) has been inserted to illustrate this point. It was carried out with only 15 ml. of charcoal, which was insufficient to separate completely the ethyl acetate and the carbon tetrachloride although all the other components are well separated. Another case is afforded by the separation of benzene (80·2°) and *cyclo*hexane (80·8°). In this case sharp steps are produced, but although the *cyclo*hexane step is pure, the benzene step contains about 10% of *cyclo*hexane. The *cyclo*hexane can be removed completely from the benzene by use of a fine charcoal, obtained by sedimentation.

In certain instances a poor separation is emphasised by an increase in the normal diffuse zone between two steps, which are themselves quite pure. Thus in the separation of thiophen (84°) and benzene (80°) the diffuse zone contains 0·10 g. instead of the normal 0·02 g. of a mixture. By use of fine charcoal the diffuse zone can be reduced again to 0·02 g. This system shows a further point of interest with a reversal of displacement order. With bromobenzene displacer and the column at 100°, the thiophen is displaced first, but with heptane displacer and the same (crude) charcoal column at 20° the benzene step precedes the thiophen step. In this case the diffuse zone contains 0·05 g. of the mixture.

In some cases it is possible to simplify the separation of close-boiling mixtures by an appropriate change of adsorbent. Thus silica gel, which has a low affinity for chloro-compounds, may be used to separate carbon tetrachloride (77·5°) and *n*-butyl chloride (78°) from other substances such as benzene (80·2°), ethyl methyl ketone (79·6°), and ethyl acetate (77·2°). The chloro-compounds appear as separate elution peaks, ahead of the steps formed by the other components.

It has also been found possible quite readily to separate other mixtures, which, though not close-boiling, are difficultly separable by normal distillation methods, *e.g.*, water and pyridine, water and toluene, and water and dioxan.

(viii) *The Problem of Closely Similar Step Heights.*—It may happen that adjacent steps in a displacement analysis are so similar in height that they are not easily distinguished from one another by the normal thermal-conductivity recorder. This is particularly the case with isomeric mixtures; *e.g.*, some of the different pentanes, hexanes, and heptanes give steps which are virtually indistinguishable from those of their isomers. Good separations are, however, effected, as has been shown by careful measurement of b. p.s (Fig. 9). Ethylbenzene forms a step which is just distinguishable from that of the xylenes, but the individual xylenes appear to form one step. Boiling point measurements again show that *o*- (144°) is clearly separated from *m*- (138·8°) and *p*-xylene (138·4°).

An interesting case of partial separation of two isomers differing only in the position of a double bond is afforded by an analysis of a mixture of 2 : 6-dimethylhepta-2 : 5- and -2 : 6-diene. Fractions were collected and analysed by infra-red measurement by L.

Bateman (British Rubber Producers' Research Association), giving the results quoted in Table 5.

TABLE 5. *Analysis of heptadienes.*

Displacer : bromobenzene		Displacer : *o*-dichlorobenzene	
Fraction	2 : 5-Diene, %	Fraction	2 : 5-Diene, %
1	5	1	5
2	35	2	5
3	45	3	40
		4	40

The problem of closely similar step heights may be solved in a number of ways. First, the sensitivity of the thermal conductivity cell can be increased. Secondly, it is possible to collect fractions for analysis as in the examples quoted above or, more conveniently, to make use of another continuous analysing device either as a substitute or as an auxiliary for the thermal-conductivity cell. It is quite easy for the gas leaving the column to flow through a number of different analysing devices in turn, and this possibility has led

FIG. 9. FIG. 10.

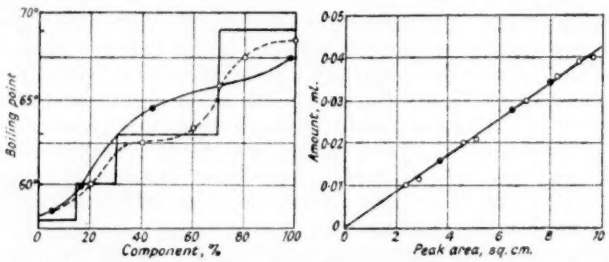


FIG. 9. *Characterisation of hexane fractions from displacement columns by means of boiling points.*

Full curve : Fractions obtained from 0·7 ml. of hexane, using 12 ml. of charcoal. Broken curve : Fractions obtained from 0·7 ml. of hexane, using 24 ml. of charcoal. Sharp steps represent ideal separation of the four isomers present : 2 : 3-*dimethylbutane* (*b. p.* 58°), 2-*methylpentane* (60°), 3-*methylpentane* (63°), *and* n-*hexane* (68°).

FIG. 10. *Quantitative analysis on partition columns.*

Plot of area under cyclo*hexane peak, against amount of* cyclo*hexane. Open circles represent elutions from silicone* (702) *column. Full circles represent elutions from nitrobenzene column.*

us to make a general investigation of alternative analysers to the thermal-conductivity cell. A review of some of this work has already been given (Griffiths, James, and Phillips, *loc. cit.*). A third method employs a marker substance, chosen so as to be displaced between the two difficultly distinguishable components. As more substances are investigated by the technique, the choice of suitable marker substances becomes easier. A simple illustration of the principle is, however, given by Analysis O (Table 2). There, it will be seen that the step heights of chloroform and chlorobenzene are sufficiently close to make it difficult to distinguish them with an insensitive thermal-conductivity cell. They are, however, separated from one another in Analysis O by the steps of ethyl acetate, thiophen, dioxan, pyridine, and butyl acetate, all of which would be suitable marker substances. Another illustration is afforded by Analysis L, where chlorobenzene acts as a marker between pyridine and *o*-xylene.

(ix) *Results obtained with the Partition Columns.*—Fig. 6 illustrates the result of a typical partition analysis. The qualitative analysis is effected by a measurement of " retention volumes," *i.e.*, the volumes of nitrogen which have to be passed through the column before the peak maxima occur. Provided the flow-rate is kept constant, these are more conveniently measured as the times before the various maxima appear. Some typical results are given in Table 6. The quantitative analysis is effected by measurement of the area under a peak, and is illustrated by the results shown in Fig. 10.

For linear partition isotherms the peaks will have a symmetrical structure, and this is generally found so long as only small amounts of the component are dissolved in the

column liquid. If larger quantities are employed, *i.e.*, if the column approaches an overloading condition, the solutions are no longer dilute, and non-linear isotherms and skew structures for the peaks may be obtained.

TABLE 6. *Partition analyses on three columns.**

Dibutyl phthalate column at 56°					Tritolyl (" tricresyl ") phosphate column at 56°				Nitrobenzene column at 15°				
Substance	Appearance of maxima (min.)				Substance	Appearance of maxima (min.)			Substance	Appearance of maxima (min.)			
	1	2	3	4		1	2	3		1	2	3	
*cyclo*Hexane	6·5	6·5	6·5	6·5	*iso*Propyl chloride	3·5	3·5	3·5	Pentane ...	3·5	3·5	3·5	
Benzene ...	14	14	14	14	*n*-Propyl chloride	5	5	5	Hexane	11·5	11·5	11·5	
Thiophen ...	19	18·5	19	19	*n*-Butyl chloride	11·5	11·5	11·5	Heptane	37	37	37	

* Run numbers are recorded above the times.

In contradistinction to the adsorption columns, the partition columns have no self-sharpening properties, so there is no tendency for small traces to concentrate, and a diffuseness once obtained is only increased along the length of the column. In consequence, some little care must be exercised in placing materials on the partition column, for if one

FIG. 11. FIG. 12.

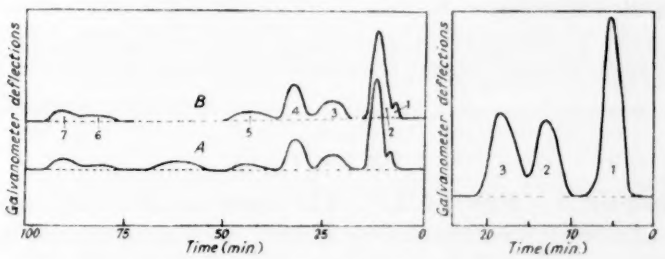


FIG. 11.

A. *Partition analysis of light petroleum fraction (b. p. 40—100°) from column of silicone* (702). B. *Composite picture constructed from separate analyses of pure hydrocarbons from same column*: (1) iso*pentane*, (2) n-*pentane*, (3) 3-*methylpentane*, (4) n-*hexane*, (5) 2-*methylpentane*, (6) 3-*methylhexane and* 2 : 3-*dimethylpentane, and* (7) n-*heptane*.

FIG. 12. *Partition analysis of* cyclo*hexane* (1), *benzene* (2), *and thiophen* (3) *from* 1·5 *ml. of dibutyl phthalate at* 56°.

component arrives in two bursts it will remain as two separate peaks during the column development. The fact that a band spreads out along the column is particularly a defect when a wide range of substances is to be separated. The later components then appear as long bands of low concentration (*e.g.*, Fig. 6). This defect may, however, be overcome by use of a column the temperature of which is rising continuously throughout the run (*idem, ibid.*). In general, retention volumes are very sensitive to column temperature, a change of approximately 10% in retention volume resulting from a 1° change in column temperature, which has therefore to be controlled carefully. Displacement columns, however, are relatively insensitive, a 1% change of column temperature producing about 0·5% change in a typical step height (Part I, *loc. cit.*).

On the other hand, because of the peak structure obtained, the partition method has decided advantages for the analysis of mixtures of isomers, or mixtures of certain close-boiling substances where the similarities of the step heights produced in the displacement method make differentiation and estimation difficult. Such an example is provided by the pentane and hexane isomers, which are readily separated on a column of silicone fluid (702) as is illustrated by Fig. 11, which represents an analysis of a light petroleum fraction (b. p. 40—100°), with the separate elution analyses of various pentanes, hexanes, and heptanes also displayed for comparison. The separation of the close-boiling *cyclo*hexane, benzene, and thiophen is illustrated in Fig. 12. Another useful feature of the partition

column is the manner in which it may sometimes be possible to alter the separations in a more or less predictable way by an appropriate change of column fluid. Thus with column lengths so chosen as to give a constant retention time of 10 min. for the *cyclo*hexane peak, the following values (min.) were obtained for benzene: 15 (silicone fluid 702), 23 (dibutyl phthalate, or tritolyl phosphate), and 37 (nitrobenzene).

Conclusion.—The results described above show that the gas-chromatographic methods are capable of effecting remarkably sharp separations of mixtures of volatile organic compounds, and that they are convenient for the analysis of small quantities of material. Quantitative analyses can be made with an accuracy of better than 1%. The two basic techniques, adsorption (displacement) and partition (elution), tend to be complementary to one another. The displacement technique produces concentrated zones, ideally suited for quantitative analysis and general preparative work. The partition method produces zones of low concentration, which are ideal for the differentiation of closely similar substances and for the sharpest separations. The adsorption columns possess self-sharpening properties, which make them useful for the isolation of trace materials, and allow good results to be obtained with only the crudest type of column packing.

Gas-chromatographic techniques should have many applications in both analytical and preparative work. We propose to employ them for the more detailed analysis of the products obtained in certain organic reactions, and also in a general investigation of volatile inorganic compounds.

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323. *Coenzyme A. Part VIII.* The Synthesis of Pantetheine 4′-Phosphate (Acetobacter Stimulatory Factor), a Degradation Product of the Coenzyme.*

By J. BADDILEY and E. M. THAIN.

Pantetheine $O^{2'}$,*S*-dibenzyl ether (III; R = H) was prepared from pantothenic acid 2′-benzyl ether (II; R = H) by reaction with ethyl chloroformate followed by 2-benzylthioethylamine. Phosphorylation with dibenzyl phosphorochloridate,† then removal of benzyl groups with sodium in liquid ammonia, gave DL-pantetheine 4′-(dihydrogen phosphate) (I).

D(+)-Pantetheine 4′-(dihydrogen phosphate) was synthesised by direct phosphorylation of pantethine with dibenzyl phosphorochloridate, followed by removal of benzyl groups with sodium in liquid ammonia, and was identical with the product obtained by the action of nucleotide pyrophosphatase or dilute acids on coenzyme A. It was converted into coenzyme A in the presence of adenosine triphosphate and an enzyme system from pigeon liver.

FROM a study of the hydrolysis products of coenzyme A it was concluded that a pantothenic acid 4′-phosphate structure was present in the molecule (Baddiley and Thain, *J.*, 1951, 2253). This was confirmed later by the isolation of the 4′-phosphate and other products from an alkaline hydrolysate (*idem*, *J.*, 1952, 3783) and on the basis of these and other findings a structural formula was given to the coenzyme. One observation, however, was not readily explained on this or any other formula, namely, the nature of a degradation product of coenzyme A which promoted growth of *Acetobacter suboxydans* (cf. King, Locher, and Cheldelin, *Arch. Biochem.*, 1948, **17**, 483). This fragment, originally produced from coenzyme A by the action of unpurified liver enzymes (Novelli, Kaplan, and Lipmann, *J. Biol. Chem.*, 1949, **177**, 97; Novelli, Flynn, and Lipmann, *ibid.*, p. 493) is a product of pyrophosphatase action (Novelli, "Phosphorus Metabolism," The Johns Hopkins Press,

* Part VII, *J.*, 1953, 903. † For nomenclature see *J.*, 1952, 5122.

Baltimore, 1951, Vol. I, p. 414). It may be formed also by short acid hydrolysis of the coenzyme and is known as the "*Acetobacter* stimulatory factor" (ASF). As it contained no adenine and gave pantothenic acid and phosphate in a ratio of about 1 : 1 on enzymic hydrolysis it was thought to be a simple phosphate of pantothenic acid. None of the synthetic monophosphates of pantothenic acid stimulated growth of *A. suboxydans*; consequently we suggested (*J.*, 1951, 2253) that ASF was pantetheine 4′-(dihydrogen phosphate) (I). Although this was questioned later (*ibid.*, p. 3421) because of indications that the active substance contained no sulphur, Novelli (personal communication) has found recently that the 2-mercaptoethylamine residue is probably still intact in ASF. In view of the difficulties of isolating such a substance in pure form from a coenzyme A hydrolysate, unequivocal synthesis of (I) was desirable. This has been achieved.

$H_2O_3PO{\cdot}CH_2{\cdot}CMe_2{\cdot}CH(OH){\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}SH$ (I)

$RO{\cdot}CH_2{\cdot}CMe_2{\cdot}CH(O{\cdot}CH_2Ph){\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$ (II)

Phosphorylation of pantothenic acid 2′-benzyl ether (II; R = H) with diphenyl phosphorochloridate in pyridine yielded a syrupy diphenyl phosphate from which the phenyl groups were removed by alkaline hydrolysis; in accordance with earlier observations on pantothenic acid phosphates (Baddiley and Thain, *J.*, 1951, 246), the amide linkage remained substantially intact during the alkali treatment. The product, $O^{2'}$-benzyl pantothenic acid 4′-phosphate (II; R = PO_3H_2), in the form of its 4-methylmorpholinium salt, was treated with ethyl chloroformate and then 2-mercaptoethylamine under conditions similar to those described in a recent synthesis of pantetheine (Wieland and Bokelmann, *Naturwiss.*, 1951, **38**, 384). The reaction appeared to be complex, however, and no recognisable products were isolated.

Attention was directed next to the phosphorylation of derivatives of pantetheine rather than of pantothenic acid. Pantothenic acid 2′-benzyl ether (II; R = H), which has been prepared by an improved method (see Experimental section), reacted smoothly with ethyl chloroformate in the presence of 4-methylmorpholine. The resulting mixed carbonic anhydride evolved carbon dioxide on treatment with 2-benzylthioethylamine, giving pantetheine $O^{2'}S$-dibenzyl ether (III; R = H) in good yield. The structure of the product was indicated by its ready reduction with sodium in liquid ammonia to pantetheine. Phosphorylation with dibenzyl phosphorochloridate in pyridine then gave a neutral syrup, presumably the tetrabenzyl compound [III; R = $PO(O{\cdot}CH_2Ph)_2$]. Removal of benzyl groups from this substance could not be effected by catalytic methods owing to the presence of sulphur in the molecule. Although it was known from the experiments recorded above that benzyloxy- and benzylthio-groups could be reduced smoothly with sodium in liquid ammonia in similar compounds, it was not known whether both benzyl groups could be removed from a dibenzyl phosphate by this method. Nor was it known whether the resulting phosphates would be stable towards the reagents. Qualitative experiments showed that both dibenzyl and diphenyl phosphate were converted into inorganic phosphate by sodium in liquid ammonia. The scope and limitations of this procedure for removing protecting phenyl and benzyl groups from organic phosphates are under investigation. Certain advantages have already been found over hydrolytic or catalytic methods with compounds containing sulphur or possessing acid-lability.

$RO{\cdot}CH_2{\cdot}CMe_2{\cdot}CH(O{\cdot}CH_2Ph){\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}CH_2Ph$ (III)

$[RO{\cdot}CH_2{\cdot}CMe_2{\cdot}CH(OH){\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}]_2$ (IV)

When [III; R = $PO(O{\cdot}CH_2Ph)_2$] in the presence of a little alcohol was treated with sodium in liquid ammonia four benzyl groups were removed and the product (I) was purified by successive conversion into lithium, silver, and finally barium salts. It was homogeneous when examined by paper chromatography in the two solvent systems described in the Experimental section and on hydrolysis yielded pantothenic acid 4′-phosphate. Examination of the crude reaction product showed the presence of pantothenic acid 4′-phosphate as the main impurity. This must have arisen through partial hydrolysis of the rather labile amide linkage between the β-alanine and 2-mercaptoethylamine residues during hydrogenolysis. Purification through the silver salt removed this contaminant. Attempts

to prepare pantetheine 4′-phosphate by phosphorylating (III; R = H) with diphenyl phosphorochloridate, with subsequent removal of phenyl and benzyl groups with sodium in liquid ammonia, gave only an impure product. Although paper chromatography of the product showed the presence of some 4′-phosphate other unidentified substances were also formed.

Pantetheine 4′-phosphate has been examined by Drs. Novelli and Lipmann with a partly purified enzyme system from pigeon liver. This is a mixture of at least two enzymes which, together and in the presence of adenosine triphosphate, are capable of synthesising coenzyme A from ASF (Levintow and Novelli, Abs. Papers, Atlantic City Meeting, Amer. Chem. Soc., 1952, p. 33c). Synthetic pantetheine 4′-phosphate showed an activity in this system equivalent to 265 units CoA/mg. which represents a conversion of 48%, in excellent agreement with the calculated 50% conversion for a DL mixture. Pantetheine 2′-phosphate and the cyclic 2′ : 4′-phosphate described in the previous paper (*J.*, 1953, 903) were inactive in this test.*

The above synthesis is unequivocal and provides a rigid proof of the structure of ASF and strong support for the proposed formula for coenzyme A. However, the product was a DL-mixture and in order to prepare moderate quantities of an optically pure material the somewhat simpler but structurally ambiguous procedure of direct phosphorylation of D(+)-pantethine (IV; R = H) was investigated. It was expected that the primary hydroxyl group at position 4′ in pantethine would be phosphorylated more readily than would the sterically hindered secondary 2′-hydroxyl group. This was shown to be so by treating D(+)-pantethine with dibenzyl phosphorochloridate in pyridine and reducing the neutral dibenzyl ester [IV; R = $PO(O{\cdot}CH_2Ph)_2$] with sodium in liquid ammonia. The product, purified through its barium and silver salts, was identical with pantetheine 4′-phosphate prepared by the first method. Its activity in the enzyme test was equivalent to 450 units CoA/mg., representing an 82% conversion. This work is being extended to include the synthesis of mixed pyrophosphates of pantetheine and adenosine more closely related to coenzyme A.

The work described in this paper completes the identification of all the monophosphates of pantothenic acid and pantetheine obtained by enzymic or chemical hydrolysis of coenzyme A. The course of acid and alkali hydrolysis is summarised briefly as follows.

The first points of attack by alkali are the pyrophosphate linkage and the amide linkage between the β-alanyl and the 2-mercaptoethylamine residue. The products at this stage are pantetheine 4′-(dihydrogen phosphate), pantothenic acid 4′-(dihydrogen phosphate), and phosphorylated derivatives of adenosine. Alternatively, intramolecular phosphorylation may result in the formation of a cyclic phosphate [pantetheine 2′ : 4′-(hydrogen phosphate)]. Further action of alkali on this gives a mixture of pantothenic acid 2′ : 4′-(hydrogen phosphate) and 4′-(dihydrogen phosphate). In acids, coenzyme A is first hydrolysed at the pyrophosphate linkage to pantetheine 4′-(dihydrogen phosphate), no internal phosphorylation being possible under these conditions. Further action of acids gives pantothenic acid 4′-(dihydrogen phosphate).

Experimental

Pantothenic Acid 2′-Benzyl Ether (II; R = H).—The following improved method is based on a recent synthesis of pantothenic acid (B.P. 660,722). During 4 hr.' refluxing, finely powdered β-alanine (2·8 g.) dissolved in a solution of pantolactone benzyl ether (6·95 g.) (Baddiley and Thain, *J.*, 1951, 246) and dimethylamine (2·5 g.) in anhydrous methanol (50 c.c.). After a further 4 hr.' refluxing, evaporation under reduced pressure gave a syrup, which was dissolved in water. Acidification with dilute sulphuric acid, extraction (3 times) with ethyl acetate, washing with water, and removal of solvent under reduced pressure gave a syrup. This was dissolved in sodium hydrogen carbonate solution, washed (3 times) with ether, then recovered by acidification with sulphuric acid and extraction (3 times) with ethyl acetate. The organic layer was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to a clear syrup (7·4 g.) (Found : C, 62·2; H, 7·6; N, 4·5. Calc. for $C_{16}H_{23}O_5N$: C, 62·2; H, 7·5; N, 4·5%).

* A preliminary account of these results has been reported already (Baddiley, Thain, Novelli, and Lipmann, *Nature*, 1953, **171**, 76).

O²′-Benzyl Pantothenic Acid 4′-(Dihydrogen Phosphate) (II; R = PO_3H_2).—The above benzyl ether (3·8 g.), dissolved in anhydrous pyridine (50 c.c.), was cooled to −20°. Diphenyl phosphorochloridate (3·63 g., 1·1 mol.) was added and the resulting solution set aside at room temperature for 20 hr. Water (3 c.c.) was added and after a further 30 min. solvent was removed by distillation under reduced pressure. The residue was dissolved in chloroform, washed twice with N-sulphuric acid, then twice with water, dried ($MgSO_4$), and freed from solvent under reduced pressure. The residual syrup was evaporated twice with benzene to remove traces of chloroform, then dissolved in 2N-sodium hydroxide (100 c.c.). Traces of organic solvents were removed by gentle warming at the water pump. After 1·5 hr.' refluxing the cooled solution was passed through Amberlite IR-120 resin (H form) to remove sodium ions. The acidic eluate was neutralised (pH 8) with barium hydroxide solution, kept at 0° for 12 hr., filtered, and concentrated under reduced pressure to about 35 c.c. This solution was passed through IR-120 and the eluate neutralised (pH 8) with barium hydroxide solution. The clear solution was evaporated to a few c.c. and acetone added to about 70% concentration. A small sticky precipitate (0·5 g.) was removed by centrifugation and a further 200 c.c. of acetone were added. The precipitate (1·95 g.) was removed by centrifugation, washed with acetone, and dried over phosphoric oxide. Evaporation of the mother-liquors yielded a further quantity of solid (0·5 g.). The pure *barium* salt (Found: N, 2·2. $C_{16}H_{21}O_8NPBa_{1·5}$ requires N, 2·4%) was homogeneous when examined by paper chromatography in *n*-propanol–ammonia (R_F 0·82). Its constitution was established by suspending a small sample in liquid ammonia, then reducing it with sodium. The insoluble barium salt was rubbed continually during the reduction. After evaporation of the ammonia the solid residue was dissolved in water and passed through a small column of IR-120 resin. The eluate was neutralised with ammonia and, after concentration, was run on paper in *n*-propanol–ammonia. A single spot was observed, having R_F 0·35, identical with pantothenic acid 4′-(dihydrogen phosphate).

Pantetheine O²′S-Dibenzyl Ether.—Ethyl chloroformate (2·4 g., 1 mol.) was added dropwise to a solution of pantothenic acid 2′-benzyl ether (6·8 g., 1 mol.) and 4-methylmorpholine (2·2 g., 1 mol.) in dry dimethylformamide (*ca.* 20 c.c.) which was cooled to −20° in acetone–solid carbon dioxide. 4-Methylmorpholine hydrochloride separated and after the addition the temperature was kept at −5° for 10 min. A chloroform solution of 2-benzylthioethylamine, prepared by liberation of the base from the hydrochloride (4·5 g., 1 mol.) with concentrated sodium hydroxide solution, extraction with chloroform (4 × 15 c.c.), and drying ($MgSO_4$), was cooled to −5° and added to the dimethylformamide solution, which caused a discrete evolution of carbon dioxide. The temperature was kept at −5° for 15 min., then set aside for 12 hr. at room temperature. Solvents were removed under reduced pressure, the residue was dissolved in chloroform (50 c.c.), washed successively with 2N-sulphuric acid (30 c.c.), water (30 c.c.), 2N-sodium hydroxide (30 c.c.), and water (30 c.c.), and dried ($MgSO_4$), and the solvent was removed by distillation under reduced pressure, yielding *pantetheine O²′S-dibenzyl ether* (8·8 g., 87%) as an almost colourless syrup (Found: C, 65·2; H, 7·6; N, 6·3. $C_{25}H_{34}O_4N_2S$ requires C, 65·4; H, 7·4; N, 6·1%).

Reduction of Pantetheine O²′S-Dibenzyl Ether to Pantetheine.—The dibenzyl ether (*ca.* 10 mg.) was dissolved in liquid ammonia (15 c.c.), and very small pieces of sodium were added until a blue colour persisted in the solution for 20 min. Excess of sodium was destroyed by gentle swirling in air, and solvent allowed to evaporate. The white, powdery residue was dissolved in water and the solution neutralised (pH 7) with dilute sulphuric acid. Solvent was removed by evaporation *in vacuo* and the residue extracted thrice with butanol. A drop of this solution was examined by paper chromatography in butanol–acetic acid–water. A spot (R_F 0·75), indistinguishable from that of pantetheine, was observed.

Pantetheine 4′-(Dihydrogen Phosphate).—Pantetheine *O²′S*-dibenzyl ether (6 g.) was dissolved in dry pyridine (20 c.c.), and the solution cooled to the f. p. in acetone–solid carbon dioxide. To the slurry was added dropwise, with shaking, a solution of dibenzyl phosphorochloridate in carbon tetrachloride prepared from dibenzyl phosphite (6·9 g., 2 mol.) (Atherton, Openshaw, and Todd, *J.*, 1945, 382). The temperature was then kept at −5° for 30 min. and the mixture finally left at room temperature overnight. As much pyridine and carbon tetrachloride as possible were removed by distillation under reduced pressure, and the residue was dissolved in chloroform (20 c.c.), washed with 2N-sulphuric acid (2 × 20 c.c.) and water (2 × 20 c.c.), and dried ($MgSO_4$). The syrup obtained on evaporation of the solvent was dissolved in methyl alcohol (10 c.c.). Liquid ammonia (60 c.c.) and then sodium, in small pieces, were added until a transient blue colour was produced. Ammonia was allowed to evaporate off, the residue dissolved in ice-cold water (50 c.c.) and extracted with ether, and the clear aqueous solution

passed through IR-120 resin (H form) to remove bases. The acid eluate was neutralised (pH 7) with lithium hydroxide and evaporated to dryness.

Purification via *the lithium and silver salts.* The crude lithium salt was triturated with methyl alcohol (100 c.c.), and the undissolved fraction removed by centrifugation; this fraction was free from halide. The methyl-alcoholic extract was diluted with ether (300 c.c.), and the precipitate collected. Since it still contained a trace of chloride ion it was redissolved in methyl alcohol (50 c.c.) and diluted with ether (200 c.c.). The precipitate was collected by centrifugation, combined with the undissolved fraction, and dried. The lithium salt was dissolved in water (50 c.c.), and acetic acid added (to pH 4), followed by silver nitrate solution until no further precipitate was formed. The yellow silver salt was collected by centrifugation and washed with water (2 × 20 c.c.), after which the washings were almost free from silver ions. The precipitate was suspended in water (50 c.c.), the solution saturated with hydrogen sulphide, excess of hydrogen sulphide removed under reduced pressure, barium hydroxide solution added to pH 7, and the precipitate of silver sulphide removed by centrifugation. The clear aqueous solution was concentrated (*ca.* 10 c.c.) under reduced pressure, and ethyl alcohol (50 c.c.) added. No precipitate was produced. Ether (200 c.c.) was added and the precipitate of the *barium* salt of pantetheine 4′-phosphate collected by centrifugation and dried (1·5 g.) (Found: C, 25·6; H, 4·7; N, 5·6; P, 6·0; Ba, 28·2. $C_{11}H_{21}O_7N_2PSBa,H_2O$ requires C, 25·8; H, 4·1; N, 5·5; P, 6·1; Ba, 26·9%).

Ascending paper chromatography of this material showed it to be homogeneous with respect to phosphorus and sulphur in the propyl alcohol–ammonia–water and *iso*butyric acid–ammonia–water solvents.

	R_F in Pr^nOH–NH_3–H_2O	R_F in $Pr^i{\cdot}CO_2H$–NH_3–H_2O
Pantothenic acid 2′ : 4′-phosphate	0·51	0·40
Pantothenic acid 4′-phosphate	0·22	0·32
Pantetheine 4′-phosphate	0·28	0·55

D(+)-*Pantetheine* 4′-(*Dihydrogen Phosphate*) (IV; R = PO_3H_2).—A brisk current of oxygen was passed through a sintered bubbler into a solution of pantetheine (3·8 g.) in pyridine (60 c.c.) until a sample no longer gave a positive nitroprusside test for thiol. Anhydrous benzene (*ca.* 30 c.c.) was added and the solution evaporated to a syrup under reduced pressure. The residue was dissolved in anhydrous pyridine (50 c.c.) and cooled to −40°. Dibenzyl phosphorochloridate (from dibenzyl phosphite, 3·6 g., 1 mol.) was added and the solution kept at −40° for 15 min. After 3—4 hours at room temperature pyridine was removed by distillation under reduced pressure and the residue dissolved in chloroform. The chloroform solution was washed with successive portions of N-sulphuric acid, water, and sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated. The residual syrup was washed thrice with benzene, during which it changed into a hard resin. The resin was dissolved in alcohol, a small amount of solid removed by centrifugation, and most of the alcohol removed by evaporation. The rather viscous solution was added to liquid ammonia (*ca.* 50 c.c.), and small pieces of sodium were added until a transient blue colour could be observed throughout the solution. Ammonia was evaporated off, and the residue dissolved in cold water (20 c.c.) and passed through IR-120 resin. The eluate was neutralised (pH 8) with barium hydroxide solution, barium phosphate removed by centrifugation, the clear solution evaporated to small volume, and the barium salt (2·0 g.) precipitated with acetone.

Purification through the silver salt. To a solution of the barium salt (1·2 g.) in water (50 c.c.) was added an excess of silver nitrate solution and the pH adjusted to 7 with dilute aqueous sodium hydroxide. The precipitated silver salt was collected by centrifugation, washed with water until washings were free from barium ions (about 4 washings were required), suspended in water, and decomposed with hydrogen sulphide. Excess of hydrogen sulphide was removed by aeration and the solution was neutralised (pH 8) with barium hydroxide solution. Silver sulphide was removed by centrifugation, and the clear supernatant liquid evaporated under reduced pressure to a very small volume. The *barium* salt of D(+)-pantetheine 4′-phosphate (probably containing some of the disulphide) (0·3 g.) was precipitated by addition of acetone and ether. A further quantity (0·6 g.) was extracted by suspending the silver sulphide precipitate in water and saturating it with hydrogen sulphide. During this treatment the precipitate decreased considerably in bulk and darkened. It was removed by centrifugation, and the supernatant liquid evaporated to small volume from which the barium salt was isolated as described above (Found: Ba, 28·3. $C_{11}H_{21}O_7N_2PSBa$ requires Ba, 27·8%). It had $[\alpha]_D^{18}$ +10·8° (*c*, 4·2 in H_2O). When examined on paper in the *iso*butyric acid–ammonia–water system it gave a

single spot (R_F 0·55), containing phosphorus and thiol and indistinguishable from pantetheine 4′-phosphate prepared as described above.

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324. 3 : 4-, 3 : 5-, *and* 3 : 6-*Dimethylcatechol.*

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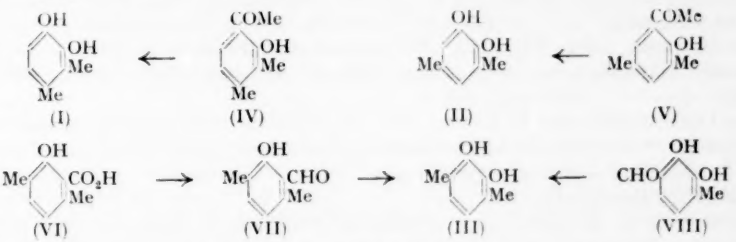
3 : 4-, 3 : 5-, and 3 : 6-Dimethylcatechol have been synthesised by the oxidation of 2-hydroxy-3 : 4-dimethylacetophenone, 2-hydroxy-3 : 5-dimethylacetophenone, and 2-hydroxy-3 : 6-dimethylbenzaldehyde respectively by hydrogen peroxide in aqueous tetramethylammonium hydroxide. 3 : 5- and 3 : 6-Dimethylcatechol have been isolated from coal tar produced by low-temperature carbonisation. Certain alkyl-catechols and -resorcinols are jointly responsible for the red colour produced when phenolic fractions of low-temperature carbonisation coal tar are dissolved in alkalis.

OF the four dimethyl catechols only the 3 : 5- (II) and 4 : 5-dimethyl derivatives were definitely known when this work was started. Since then Loudon and Scott (*J.*, 1953, 268) have synthesised 3 : 6-dimethylcatechol (III). Further investigation of the properties of (II) and (III), and the preparation of 3 : 4-dimethylcatechol (I), are of interest, since it was probable that (I) and (III) might occur in low-temperature carbonisation coal tar.

Burke and Caplan (*J. Ind. Eng. Chem.*, 1927, **19**, 34) observed that certain phenolic fractions of low-temperature carbonisation coal tar gave red solutions in aqueous alkalis. The substance, or substances, responsible for the red colour were isolated by extraction into aqueous borax (a characteristic property of catechols), and from this solution they were liberated by acidification and obtained finally as a colourless oil, b. p. 256°/760 mm., 116—117°/2 mm., which yielded an intensely red solution in aqueous sodium hydroxide. Analysis of the oil established the formula $C_8H_{10}O_2$, and, by excluding the known ethyl- and 3 : 5- and 4 : 5-dimethyl-catechol, they concluded that it must be the unknown 3 : 4- or 3 : 6-dimethylcatechol.



We have now synthesised 3 : 4-dimethylcatechol (I), m. p. 84—85°, and find that it dissolves in 1% aqueous sodium hydroxide to a deep, brownish-red solution. The colour slowly becomes browner, and is due to oxidation since only a faint yellow is produced in the absence of oxygen, but when such a solution is shaken with air the brownish-red colour develops rapidly. We have also prepared 3 : 6-dimethylcatechol (III), m. p. 101°, by two methods differing from that used by Loudon and Scott, and find that it gives a purple solution in alkalis in presence of air. We conclude that the material isolated by Burke and Caplan may have contained 3 : 4-dimethylcatechol, but the presence of other, probably isomeric compounds is suggested by the fact that their product did not solidify even at low temperatures, and by other considerations discussed in the sub-section below.

The synthesis of 3 : 4-dimethylcatechol (I) was achieved as follows. 2-Hydroxy-3 : 4-

dimethylacetophenone (IV) was prepared from 2 : 3-dimethylphenyl acetate by reaction with aluminium chloride. This ketone (IV) was then oxidised by hydrogen peroxide in aqueous tetramethylammonium hydroxide (3 equivalents), giving 3 : 4-dimethylcatechol (I) in 25% yield. When the oxidation was carried out in aqueous potassium hydroxide the yield was only 2·5%, and mixtures of potassium hydroxide and tetramethylammonium hydroxide gave intermediate yields of (I). This is a further instance of the advantage of using tetramethylammonium hydroxide as alkali in certain Dakin oxidations, in order to obtain ionised, rather than covalent, salts (Baker, McOmie, and Ulbricht, *J.*, 1952, 1825). When benzyltrimethylammonium hydroxide (Triton B) was used the yield of (I) was 18%.

3 : 5-Dimethylcatechol (II) was prepared in a similar manner from 2 : 4-dimethylphenyl acetate. The Fries rearrangement with aluminium chloride gave 2-hydroxy-3 : 5-dimethylacetophenone (V), and oxidation of this *o*-hydroxy-ketone with hydrogen peroxide in aqueous tetramethyl ammonium hydroxide gave 3 : 5-dimethylcatechol (II). The oxidation was unsuccessful when sodium hydroxide was used as the alkali. The substance gave a solid diacetyl derivative.

3 : 6-Dimethylcatechol (III) cannot be prepared from 2 : 5-dimethylphenyl acetate by a similar series of reactions, because the Fries rearrangement is accompanied by extensive migration of a methyl group with formation of 2-hydroxy-3 : 5-dimethylacetophenone (Auwers, Bundesmann, and Wieners, *Annalen*, 1926, **447**, 162). Hence attention was turned to 2-hydroxy-3 : 6-dimethylbenzaldehyde (VII) which has been prepared in 4% yield by the Gattermann reaction (Anselmino, *Ber.*, 1902, **35**, 4099; Clemo, Haworth, and Walton, *J.*, 1929, 2376). Formylation of *p*-xylenol with hexamine in acetic acid (Duff and Bills, *J.*, 1934, 1305) gave a 21% yield of 4-hydroxy-2 : 5-dimethyl*iso*phthalaldehyde, and formylation with hexamine in glycerol–glyceroboric acid (Duff, *J.*, 1941, 547) gave 7% of the dialdehyde. Small yields of the dialdehyde were also obtained by the Gattermann reaction using zinc cyanide, and, accompanied by 1% of the monoaldehyde (VII), by the Tiemann–Reimer reaction. As these methods were unsatisfactory, *p*-xylenol was submitted to the Kolbe reaction, giving 2-hydroxy-3 : 6-dimethylbenzoic acid (VI); this was then reduced with sodium amalgam in presence of boric acid and *p*-toluidine, and the resulting Schiff's base hydrolysed (method of Weil, *Ber.*, 1908, **41**, 4147) giving the aldehyde (VII) in 40% yield from the acid (VI). Finally (VII) was submitted to the Dakin oxidation in presence of tetramethylammonium hydroxide, giving 3 : 6-dimethylcatechol (III) in 74% yield.

The 2-hydroxy-3 : 6-dimethylbenzoic acid (VI), m. p. 195°, was identical with that prepared in a different manner by Stollé and Knebel (*Ber.*, 1921, **54**, 1220), but differed from the acid, m. p. 137°, prepared by Oliveri by heating *p*-xylenol and sodium in carbon dioxide (*Gazzetta*, 1882, **12**, 166). The nature of this latter product is unknown (see Beilstein, " Handbuch der organischen Chemie," 4th Edn., 2nd. Suppl., 1949, Vol. IV, p. 163).

3 : 6-Dimethylcatechol (III) was also prepared from 3-methylcatechol, which when formylated by the hexamine–glyceroboric acid method (Duff, *loc. cit.*) gave a small yield of 2 : 3-dihydroxy-4-methylbenzaldehyde (VIII). Clemmensen reduction then gave 3 : 6-dimethylcatechol (III).

Observations on the Red Colour of Alkaline Solutions of Phenols from Low-temperature Carbonisation Processes.—The higher fractions of such phenols, when dissolved in dilute aqueous sodium hydroxide, rapidly develop red colours when shaken in air. This holds for the whole range of phenols boiling above 260°, and indicates that more than one compound is responsible. Burke and Caplan (*loc. cit.*) concluded that the colour reaction was due to catechols, since if these substances are removed by alkali borates the reaction is not given. This work has been confirmed, and a patent (B.P. 621,639) describes a process for removing the substances responsible for the red colour, based on extraction with alkali borates.

Catechols alone do not give the red colour reaction; 3 : 4-dimethylcatechol (I), however, gives a red-brown colour, but this substance has not yet been found in coal tar. Five pure catechols, all isolated from coal tar, produced by low-temperature carbonisation, were tested with dilute alkali, but none gave the red colour observed with the phenolic

fraction of coal tar; these were catechol, 3- and 4-methylcatechol, and 3 : 5- and 3 : 6-dimethylcatechol. Eventually, it was found that the typical colour reaction is produced by the simultaneous oxidation of certain catechols and a resorcinol in alkaline solution. From the limited information available it appears that, in order to give the colour reaction, the catechol must have a methyl group in a position *para* to one or other of the hydroxyl groups. The structure of the resorcinol is not critical, though it was deduced, from six resorcinols tested with 4-methylcatechol, that additional methyl groups tend to modify the colour from orange to red. Again, the colours produced with resorcinols and 3 : 5-dimethylcatechol are redder than those obtained with 4-methylcatechol. Thus simultaneous oxidation of 2 : 4-dimethylresorcinol and 3 : 5-dimethylcatechol in alkaline solution gave a crimson colour. 3-Methylcatechol and 3 : 6-dimethylcatechol gave no red or orange colour with any of the alkylresorcinols yet tested.

The test is carried out by dissolving a small quantity of the resorcinol in 1% aqueous sodium hydroxide, adding the catechol, and shaking the mixture with access to air. If first the catechol is added to the alkali, blue or brown colours result, and the red colour is masked or not produced. Addition of stronger alkali tends to give orange colours; dilution with water accentuates the red colour.

Experimental

2-Hydroxy-3 : 4-dimethylacetophenone (IV).—This ketone (b. p. 145—148°/26 mm.) was prepared in 90% yield by heating 2 : 3-dimethylphenyl acetate (4 mols.) at 155—165° for 1½ hr. with aluminium chloride (5 mols.), and distilling the product in steam after addition of dilute hydrochloric acid. The procedures of Auwers and Mauss (*Annalen*, 1928, **460**, 240) and of Smith and Opie (*J. Org. Chem.*, 1941, **6**, 427) gave 60 and 69% yields respectively.

3 : 4-Dimethylcatechol (I).—2-Hydroxy-3 : 4-dimethylacetophenone (IV) (3 g., 1 mol.) was dissolved in 10% aqueous tetramethylammonium hydroxide (44 c.c.; 3 mols.) at room temperature, and 6% aqueous hydrogen peroxide (14·5 c.c., 1·25 mol.) added in an atmosphere of nitrogen. After 2 min. a slow rise of temperature to 48° occurred (10 min.), and after ½ hr. the solution was warmed to 50° and allowed to cool. Acidification with dilute sulphuric acid gave crude unchanged ketone which was removed by shaking with light petroleum (b. p. 60—80°), and the aqueous layer then extracted with warm ethyl acetate (5 × 20 c.c.). The ethyl acetate extracts yielded a dark oil which partly solidified; this was extracted with light petroleum (b. p. 60—80°; 2 × 50 c.c.), and the extracts were concentrated, giving *3 : 4-dimethylcatechol* (I), which, after several recrystallisations from light petroleum (b. p. 40—60°), had m. p. 84—85° (yield 25%) (Found: C, 69·7; H, 7·0. $C_8H_{10}O_2$ requires C, 69·5; H, 7·2%). An alcoholic solution of this catechol derivative is coloured intensely blue-green on addition of a little aqueous ferric chloride, and the colour changes to yellow-brown on dilution with water. When this compound (I) was first isolated and crystallised from light petroleum (b. p. 40—60°) it was obtained in needles which melted sharply at 61° and liquefied in contact with a little water. It was later always obtained with the higher m. p., and this more stable probably dimorphic form does not liquefy in contact with water.

The *diacetyl* derivative separates from light petroleum (b. p. 60—80°) in compact prisms, m. p. 89—90° (Found: C, 64·9; H, 6·1. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%). The *dibenzoyl* derivative, prepared by reaction with benzoyl chloride (3 mols.) in pyridine, separates from ethyl acetate in flat prisms, m. p. 127—128° (Found: C, 76·5; H, 5·3. $C_{22}H_{18}O_4$ requires C, 76·3; H, 5·2%).

1 : 2-Dimethoxy-3 : 4-dimethylbenzene.—The catechol (I) was boiled in acetone with excess of methyl sulphate and potassium carbonate for 10 hr. The acetone-soluble product was distilled 3 times, giving a very pale yellow liquid, b. p. 70—72°/0·3 mm. [Found: C, 72·6; H, 8·3; OMe, 38·2. $C_8H_8(OMe)_2$ requires C, 72·3; H, 8·4; OMe, 37·4%].

3 : 5-Dimethylcatechol (II).—2-Hydroxy-3 : 5-dimethylacetophenone (V) (m. p. 53—54°) was prepared in 38% yield from 2 : 4-dimethylphenylacetate by the Fries rearrangement (Auwers, Lechner, and Bundesmann, *Ber.*, 1925, **58**, 45). To this ketone (V) (6 g., 1 mol.) in 10% aqueous tetramethylammonium hydroxide (88 c.c., 3 mols.) was added at room temperature 6% aqueous hydrogen peroxide (29·2 c.c., 1·25 mols.) in an atmosphere of nitrogen. The temperature rose to 54° (5 min.) and after ½ hr. the solution was warmed to 55° and allowed to cool. Acidification precipitated unchanged ketone, and the filtered solution was extracted with warm ethyl acetate (4 × 50 c.c.), yielding a dark oil. This was extracted with hot light petroleum (b. p. 60—80°;

2 × 50 c.c.), yielding, after several crystallisations from the same solvent, 3 : 5-dimethylcatechol (II) (25%), needles, m. p. 70—71° (Found : C, 69·3; H, 7·1. Calc. for $C_8H_{10}O_2$: C, 69·5; H, 7·2%). An alcoholic solution of (II) became olive-green on addition of a trace of aqueous ferric chloride, and the colour became yellow on addition of more water. 3 : 5-Dimethylcatechol was previously prepared by Hodgkinson and Limpach (*J.*, 1893, **63**, 108) and by Caldwell and Thompson (*J. Amer. Chem. Soc.*, 1939, **61**, 2354) who employed other processes.

The *diacetyl* derivative, prepared by heating (II) with acetic anhydride and a trace of pyridine, separates from light petroleum (b. p. 40—60°) as cubes, m. p. 59—60° (Found : C, 64·8; H, 6·2. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%).

2-Hydroxy-3 : 6-dimethylbenzoic Acid (VI) [with Mr. A. J. Price].—To *p*-xylenol (50 g.) in boiling xylene (400 c.c.) was added at intervals sodium (21 g.) in small portions (6 hr.) whilst a vigorous stream of carbon dioxide was delivered near the bottom of the flask. Passage of carbon dioxide at the b. p. was continued for a further 15 hr., unchanged sodium destroyed with 90% ethanol, the mixture poured into water (400 c.c.), and the aqueous layer acidified. The precipitated 2-hydroxy-3 : 6-dimethoxybenzoic acid separated from a mixture of ethanol (180 c.c.) and water (250 c.c.) in needles (20 g., 27%), m. p. 195° (Stollé and Knebel, *loc. cit.*, gave m. p. 195°). It gives a dark violet-blue ferric chloride reaction in alcoholic solution, which acquires a violet tinge on dilution with water.

2-Hydroxy-3 : 6-dimethylbenzaldehyde (VII).—The preceding acid (VI) (2·5 g., 1 mol.) was neutralised with warm, 5% aqueous sodium carbonate and then diluted (to 150 c.c.), *p*-toluidine (2·5 g., 1·5 mols.) added, and the mixture warmed to obtain a clear solution which was vigorously shaken and cooled. Sodium chloride (40 g.) and boric acid (2·5 g.) were next added, the mixture was stirred, and 2% sodium amalgam (*ca.* 150 g.) was added gradually (3 hr.), with addition of more boric acid at intervals to keep the solution faintly acid. When all the amalgam had reacted the mixture was decanted from the mercury and filtered, and to the solid was added 2N-hydrochloric acid (100 c.c.) to hydrolyse the arylidene-*p*-toluidine, and the whole was steam-distilled. The distillate yielded to ether a solid which was crystallised from light petroleum (b. p. 40—60°), giving 2-hydroxy-3 : 6-dimethylbenzaldehyde as yellow needles, m. p. 61—62° (*locc. cit.*, m. p. 62—63°).

2 : 3-Dihydroxy-4-methylbenzaldehyde (VIII).—Anhydrous glycerol (30 g.) and boric acid (7 g.) were heated for ½ hr. at 170°, hexamine (5 g.) and 3-methylcatechol (5 g.) were then added, and the mixture was kept at 150° for ¼ hr. After addition of concentrated sulphuric acid (6 c.c.) in water (20 c.c.), steam-distillation and extraction of the distillate (2 l.) with ether gave a solid which was crystallised from light petroleum (b. p. 80—100°), giving *2 : 3-dihydroxy-4-methylbenzaldehyde* (0·37 g.) as yellow needles or cubes (dimorphic), m. p. 85° (Found : C, 63·4; H, 5·2. $C_8H_8O_3$ requires C, 63·3; H, 5·3%). Its alcoholic solution gives an intense blue-green colour with ferric chloride. The colour and steam-volatility of this catechol derivative are characteristic of 2 : 3-dihydroxy-carbonyl compounds in general (see Baker and Smith, *J.*, 1936, 346).

3 : 6-Dimethylcatechol (III).—(a) *By oxidation of 2-hydroxy-3 : 6-dimethylbenzaldehyde* (VII). The aldehyde (VII) (1 g., 1 mol.) was dissolved in warm 10% aqueous tetramethylammonium hydroxide (18·5 c.c., 3 mols.), and 6% aqueous hydrogen peroxide (4·8 c.c., 1·25 mols.) added in an atmosphere of nitrogen. An exothermic reaction set in (temp. rise to 40°); the solution was later heated to 50°, and when cold was acidified with dilute sulphuric acid, filtered, and extracted with hot ethyl acetate (3 × 30 c.c.). The extracts yielded a dark brown solid which was extracted with light petroleum (b. p. 60—80°; 2 × 20 c.c.), and the extracts were concentrated, giving 3 : 6-dimethylcatechol as fine needles (74%), which after several recrystallisations from light petroleum had m. p. 101° (Found : C, 69·1; H, 7·0. Calc. for $C_8H_{10}O_2$: C, 69·5; H, 7·2%). Its alcoholic solution gave an olive-green colour with a trace of aqueous ferric chloride, and the colour becomes brown on the addition of water. The *dibenzoyl* derivative crystallised from alcohol as rhombs, m. p. 101° (Found : C, 76·0; H, 5·0. $C_{22}H_{18}O_4$ requires C, 76·3; H, 5·2%). 3 : 6-Dimethylcatechol prepared by Loudon's method (*loc. cit.*) has m. p. 104°, and a mixed m. p. was 101—102°.

(b) *By reduction of 2 : 3-dihydroxy-4-methylbenzaldehyde* (VIII). The aldehyde (VIII) (0·35 g.) was boiled for 2 hr. with concentrated hydrochloric acid (7 c.c.), water (3 c.c.), and spongy amalgamated zinc (2 g.). Extraction with ether and crystallisation of the product first from toluene and then from light petroleum gave 3 : 6-dimethylcatechol (0·10 g.), m. p. and mixed m. p. 100°.

Isolation of 3 : 5-Dimethylcatechol (II) *from Coal Tar derived from Low-temperature Carbonisation.*—A phenolic fraction (915 g.), b. p. *ca.* 261°, of the tar, consisting mainly of

monohydric phenols, was shaken at 45° with butyl acetate (900 c.c.) and an aqueous solution (400 c.c.) containing boric acid (40 g.) and sodium hydroxide (24 g.), which removed all the catechols from the organic layer. The aqueous layer was acidified, cooled, and filtered, and the residual boric acid, contaminated with a brown oil, was washed with a little ether (washings A). The aqueous filtrate was shaken with light petroleum (b. p. 100—120°) (80 c.c.), giving 3 layers. The dark, intermediate layer was mixed with the washings (A) and distilled in *vacuo*, giving a viscous, pale yellow liquid (16 g.). The lowest, aqueous layer was extracted with ether and the product distilled in *vacuo*, giving an oil (5 g.) which solidified. Crystallisation of the distilled oil from the intermediate layer was induced by seeding with this solid. The united solids were washed with a little toluene and crystallised from this solvent, giving **3** : 5-dimethylcatechol (6·6 g.) as colourless cubes, m. p. and mixed m. p. 71° (Found : C, 69·4; H, 7·4. Calc. for $C_8H_{10}O_2$: C, 69·5; H, 7·3%). It separates from water in needles. The diacetyl derivative had m. p. and mixed m. p. 59—60° (Found : C, 64·6; H, 6·1%).

Isolation of **3** : **6**-*Dimethylcatechol* (III) *from Coal Tar derived from Low-temperature Carbonisation.*—The phenolic fraction, b. p. 244—249°, of the tar consists chiefly of monohydric phenols, but the presence of catechol derivatives was shown by the formation of a white precipitate on addition of aqueous lead acetate to an alcoholic solution of the mixed phenols. This fraction (1535 g.) and benzene (700 c.c.) was shaken with 3 portions (200, 100, and 100 c.c.) of an aqueous solution containing boric acid (16% wt./vol.), and sodium hydroxide (10% wt./vol.), which completely removed the catechols from the benzene layer (lead acetate test). The combined borate extracts were acidified, extracted with ether, and distilled in *vacuo*, giving a colourless oil (110 g.) miscible with water; it solidified when seeded with 3-methylcatechol. Crystallisation from toluene gave several crops of 3-methylcatechol (cubes) (70 g.), and the final mother-liquor when kept for several days deposited both 3-methylcatechol and needle-shaped crystals which were separated by hand and recrystallised from toluene. This substance (0·2 g.), m. p. 100°, alone or when mixed with **3** : 6-dimethylcatechol (III), showed all the properties of (III) described above. A further amount (1 g.) of **3** : 6-dimethylcatechol (III) was obtained from the toluene mother-liquors by repeated shaking with water, the other catechols being preferentially extracted; concentration of the toluene solution gave crystalline (III).

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325. *Lipoid–Water Partition Coefficients of Some Aromatic Bases.*

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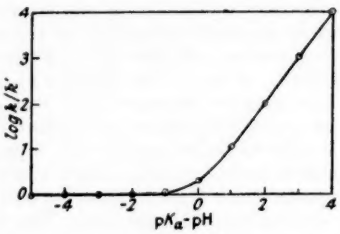
The partition coefficients between liquid paraffin and aqueous phosphate buffer (pH 7·2) were determined by a spectrophotometric method for 26 aromatic bases exhibiting tuberculostatic activity.

ONE of the factors influencing the permeability of a cell membrane to a drug molecule must be the lipoid–water partition coefficient of the drug. In order to discover the effect of variation in partition coefficient on antituberculous activity, this constant has been determined for a number of aromatic amines. The substances were bases of pK_a values ranging from 3 to 10, and the two phases were liquid paraffin and an aqueous buffer solution of pH 7·2 (the physiological pH).

Albert, Goldacre, and Heymann (*J.*, 1943, 651) and Hammick and Mason (*J.*, 1950, 348) used a colorimetric method for the determination of the partition coefficients of acridines, whereas Golumbic *et al.* (*J. Amer. Chem. Soc.*, 1949, **71**, 2624; 1950, **72**, 4145; 1951, **73**, 3966) employed a spectrophotometric technique for phenols and amines, estimating the concentration of organic material in the lipoid phase. In the present work it was found more convenient to use spectrophotometric estimation of the organic base in the aqueous phase.

The partition coefficient k of a base distributed between two immiscible liquids is given by $k = [B]_0/[B]_w$, where $[B]_0$ and $[B]_w$ are the concentrations of the undissociated base in the two phases. The base in the aqueous phase dissociates according to $[B]_w[H^+]/[BH^+] = K_a$, where K_a is the acid dissociation constant of the base. The apparent partition constant k', which is actually measured, is given by $k' = [B]_0/([B]_w + [BH^+])$. At constant hydrogen-ion concentration the degree of dissociation of the base is constant and independent of the concentration. The relation between the apparent and the true partition coefficient then becomes $k/k' = 1 + [H^+]/K_a$, *i.e.*, the apparent partition coefficient is constant at constant pH and proportional to the true value of k. A similar derivation has been used by Craig (*J. Biol. Chem.*, **1943**, **150**, 33).

If pK_a of the base is known, the true value of k can readily be calculated from $k/k' = 1 +$ antilog ($pK_a -$ pH). The ratio k/k' can be obtained from the figure, which indicates that a linear relation is obtained when the unity term in the last equation is



negligible in comparison with the antilog term, *i.e.*, when the base is substantially ionised. Such linear relation have been obtained by Hammick and Mason (*loc. cit.*) and Golumbic *et al.* (*loc. cit.*).

Method.—Dilute solutions of the salts were prepared by dissolving the pure hydrochloride of the base in M/500-phosphate buffer solution of pH 7·2 (Clark, " The Determination of Hydrogen Ions," Baillière, Tindall, and Cox, London, 1928, p. 210), the concentrations (*ca.* 1—10 mg. per 100 c.c. of soluton) being such as to give an optical density of 0·4—0·9 at the ultra-violet absorption maximum. The pH of the solution was checked on a Leeds and Northrup Universal pH meter. Known volumes of the hydrochloride buffer solution (v_w) and of liquid paraffin (B.P., 1932) (v_o) were equilibrated by mechanical shaking for 3 hours; this was sufficient for complete equilibration. After separation and centrifugation, the optical density of the aqueous layer was redetermined at the wave-length of maximum absorption which was always unchanged. The optical readings were taken on a Beckman quartz spectrophotometer, model DU, and the experiments were carried out at 20° ± 2°. If d_1 and d_2 are the initial and final maximum optical densities of the aqueous solutions, then (on the assumption that all the compounds investigated obey Beer's law), k' is given by $k' = v_w(d_1 - d_2)/v_o d_2$.

The maximum optical densities were measured at the nearest millimicron and the slit width kept constant for the initial and final solution. The volumes of paraffin and water were chosen to give a final maximum optical density in the aqueous phase of 0·15—0·6; the ratio 1 : 1 was, however, never exceeded as larger volumes of paraffin made equilibration difficult. Duplicate readings at different concentrations agreed within 5%. At the low concentrations used, the possibility of molecular association in the paraffin layer was negligible; this assumption was justified by the constancy of the values obtained for k' over a range of concentrations.

Results and Discussion.—The results, together with the ultra-violet absorption maxima, are given in Tables 1, 2, and 3. Table 1 comprises primary aromatic amines, all weakly basic with $pK_a < 7$, and substantially un-ionised at pH 7·2. Lipophilic character is seen to increase with molecular complexity, as expected. The abnormally low value of k' for compounds 1 and 4 is probably caused by the heterocyclic substituent. Table 3 contains heterocyclic bases, all with $pK_a > 7$ and therefore appreciably ionised at pH 7·2. This is indicated by the low values for k' for compounds similar in size to those in Table 1. The degree of dissociation, however, is by no means the only factor determining the magnitude

of k'. Thus, although the introduction of a methyl group into a base has a base-strengthening effect, compound 22 has a higher partition coefficient than no. 21. The same applies to compounds 24, 25, and 26, where k' again increases with increasing numbers of methyl substituents and hence increasing pK_a. This abnormal behaviour of the methyl homologues is probably due to the solubilising properties of the methyl group causing an increase in k' greater than the decrease occasioned by the inductive ($-I$) effect of the alkyl group; this behaviour may be similar in nature to the effect of methyl substituents on the ionisation and water-solubilities of *p*-aminobenzenesulphonamidopyrimidines (Gilligan and Plummer, *Proc. Soc. Exp. Biol. Med.*, **1943**, **53**, 142; Albert, "Selective Toxicity," Methuen, London, 1951, p. 36).

TABLE 1.

No.	Hydrochloride of	k'	$\lambda_{max.}$ (mμ)	No.	Hydrochloride of	k'	$\lambda_{max.}$ (mμ)
1	*p*-2-Pyridylaniline [1] ...	0·47	293	7	β-Naphthylamine	9·5	234
2	*o*-Aminophenol [2]	<1	229	8	α-Naphthylamine	9·7	237
3	*p*-Aminophenol [2]	<1	231	9	2-*Aminofluorene* [4]	57	280
4	*p*-Piperidinoaniline [3] ...	1·28	242	10	9-Aminophenanthrene [5]	72	250
5	*p*-Toluidine	2·00	233	11	2-*Aminochrysene* [6]	—	—
6	*p*-Chloroaniline	3·14	239				

[1] Dihydrochloride, m. p. 310—313° (decomp.). Forsyth and Pyman (*J.*, 1926, 2912) give m. p. > 310°. [2] Approx. only, as the compound showed pronounced oxidation in the aqueous phase. [3] Dihydrochloride (Bauer and Cymerman, *J.*, 1950, 2078). [4] Plates (from methanol), m. p. 321—322° (decomp.) (Found: N, 6·8. $C_{13}H_{11}N,HCl$ requires N, 6·45%). This salt rapidly lost hydrogen chloride when heated *in vacuo*. [5] M. p. 278—280° (decomp.). Schmidt and Strobel (*Ber.*, 1901, **34**, 1461) give m. p. 275° (decomp.). [6] Plates (from methanol), m. p. 274—275° (decomp.) (Found: N, 5·3. $C_{18}H_{13}N,HCl$ requires, N, 5·0%). Measurement of k' impossible owing to insolubility in water.

TABLE 2.

No.	Compound	k'	$\lambda_{max.}$ (mμ)
12	*N'*-4-Diphenylyl-*NN*-diethylethylenediammonium dichloride [1]	44·7	282
13	*N'*-4-Diphenylyl-*NN*-diethyl-*NN'N'*-trimethylethylenediammonium diiodide	0·065	225
14	*N*-4'-Diphenylyl-2-morpholinoethylammonium dichloride [1]	74·9	285
15	*N*-4'-Diphenylyl-*N*-methyl-2-morpholinoethylamine dimethiodide [1]	0·16	224
16	4-2''-Diethylaminoethoxydiphenyl hydrochloride [1]	104	257
17	4-2''-Diethylaminoethoxydiphenyl methiodide [1]	0·12	259
18	*N*-4-Diphenylyltrimethylammonium iodide [2]	0·04	228
19	4-Benzylamino-4'-dimethylaminodiphenyl dihydrochloride [1]	45·0	273

[1] Bauer, Cymerman, and Sheldon, *J.*, 1951, 2342. [2] Vorlander, *Ber.*, 1925, **58**, 1893.

TABLE 3.

No.	Hydrochloride of	M. p.	Formula	Found: N (%)	Required: N (%)	k'	$\lambda_{max.}$ (mμ)
20	4-*Aminoquinoline* [1]	308°	$C_9H_8N_2,HCl$	15·5	15·5	0·02	230
21	5-Aminoacridine	—	—	—	—	0·15	259
22	5-Amino-1-methylacridine	—	—	—	—	0·19	260
23	5-*Amino*-1 : 2-*benzacridine* [2] ...	380 (dec.)	$C_{17}H_{12}N_2,HCl$	10·05	10·0	4·90	286
24	9-*Aminophenanthridine*	309	$C_{13}H_{10}N_2,HCl$	12·3	12·15	3·10	240
25	9-*Amino*-3-*methylphenanthridine*	349—350	$C_{14}H_{12}N_2,HCl$	11·8	11·4	8·30	241
26	9-*Amino*-1 : 3-*dimethylphenanthridine*	372 (dec.)	$C_{15}H_{14}N_2,HCl$	11·2	10·8	47·0	242

[1] Plates (from methanol), anhyd. after drying at 120°. In air, it formed a *monohydrate* (Found: N, 14·2. $C_9H_8N_2,HCl,H_2O$ requires N, 14·15%). [2] Pale yellow plates from methanol.

Table 2 shows the large (approximately thousand-fold) drop in k' which occurs on going from a base to the methiodide in these compounds.

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326. *The Dipole Moments of Furan and Thiophen measured in the Dissolved and in the Gaseous State.*

By B. Harris, R. J. W. Le Fèvre, and E. P. A. Sullivan.

The magnitudes of μ_{gas} and $\mu_{benzene}$ of furan and thiophen are found to agree, qualitatively for furan and quantitatively for thiophen, with equations (1), (2), and (4) listed previously by Buckingham and Le Fèvre (*J.*, 1952, 1932). An analysis of the observed dielectric constants, densities, and refractive indexes of solutions in benzene supports various suggestions made by Guggenheim and by Smith. Consequent changes are indicated in the routine procedures to be used here for obtaining $_{\infty}P_2$.

Our recent communications on molecular polarity have discussed, *inter alia*: (*a*) the calculation of the total polarisation of a solute at infinite dilution from a set of dielectric constant, density, and composition data covering a range of concentrations of a given substance in one solvent, and (*b*) the devising of relations whereby "apparent" moments measured in solution may be converted into the "true" values observed for the gaseous state. For (*a*), we refer principally to a paper by Le Fèvre (*Trans. Faraday Soc.*, 1950, **46**, 1) giving our methods of computation and comparing them with those of other groups of workers. On (*b*) we cite particularly Buckingham and Le Fèvre's equations (*J.*, 1952, 1932) based partly on previous work (*J.*, 1950, 276, 283, 290, 295, 556, 1829, 2166, 3370; 1951, 2583; 1952, 1643 1649 1651; *Trans. Faraday Soc.*, 1947, **43**, 374; 1950, **46**, 812; 1951, **47**, 357.

Following Le Fèvre's paper, three others bearing on topic (*a*) have appeared (Smith, *Trans. Faraday Soc.*, 1950, **46**, 394; Everard, Hill, and Sutton, *ibid.*, p. 417; Guggenheim, *ibid.*, 1951, **47**, 573). All accept that the molecular polarisation of a solute at infinite dilution should be computed with quantities actually measured rather than extrapolated from the partial polarisations derived from individual solutions *via* earlier mixture "rules" (such as $P_{12} = P_1w_1 + P_2w_2$). Minor differences between the authors concern the modes of concentration dependence to be best assumed for ε_{12} and d_{12}: on one hand, Sutton and his colleagues take *straight-line* relations for ε_{12} or v_{12} (specific volume of solution) versus w_2; on the other, Le Fèvre, Smith, and Guggenheim prefer to regard these as, in general, *curved*, although many sets of data lead to only very slight curvature. Ultimately in either case values of $[(\varepsilon_{12} - \varepsilon_1)/w_2]_{w_2=0}$, $[(v_{12} - v_1)/w_2]_{w_2=0}$, or $[(d_{12} - d_1)/w_2]_{w_2=0}$, etc., are required.* Accordingly, Le Fèvre (*loc. cit.*) wrote $\varepsilon_{12} = \varepsilon_1(1 + \alpha w_2 + \alpha' w_2^2)$, so that $[(\varepsilon_{12} - \varepsilon_1)/w_2]_{w_2} = \alpha\varepsilon_1 + \alpha'\varepsilon_1 w_2$. Similar expressions were set up for d_{12}. The quotients on the left-hand sides of these equations should have been therefore—whenever α' was not zero—rectilinear against w_2, so that $\alpha\varepsilon_1$ (or βd_1) could be determined by the method of least squares. Guggenheim (personal communications, and *Trans. Faraday Soc.*, 1951, **47**, 573) has criticised the last step on the ground that minimising $\Sigma[(\varepsilon_{12} - \varepsilon_1 - \alpha\varepsilon_1 w_2 - \alpha'\varepsilon_1 w_2^2)/w_2]^2$ unduly weights the measurements of lower accuracy at higher dilutions. We concur, and in future work intend to fit observations of $\delta\varepsilon = \varepsilon_{12} - \varepsilon_1$ (or $\delta d = d_{12} - d_1$) to formulæ of the type $\delta\varepsilon = \alpha w_2 + b w_2^2$. The constant a will then be $(\alpha\varepsilon_1)_{w_2=0}$ or $(\beta d_1)_{w_2=0}$, respectively, for the variation of ε_{12} or d_{12} with w_2.

Both Guggenheim (*Trans. Faraday Soc.*, 1949, **45**, 715; *loc. cit.*) and Smith (*loc. cit.*) have described the estimation of orientation polarisations at infinite dilution, $_{\infty}(_{O}P_2)$, by methods which do not appear to involve the accurate measurement of densities. Thus, if the limiting values at $w_2 = 0$ of $\delta\varepsilon/w_2$ and $\delta n^2/w_2$ (n being the refractive index) are $\alpha\varepsilon_1$ and γn_1^2, Smith's proposal leads to $_{\infty}(_{O}P_2) = 3M_2v_1[\alpha\varepsilon_1/(\varepsilon_1 + 2)^2 - \gamma n_1^2/(n_1^2 + 2)^2]$. However, this simplification involves an error which can be assessed by subtracting from *e.g.*, Halverstadt and Kumler's equation (*J. Amer. Chem. Soc.*, 1942, **64**, 2988) for $_{\infty}P_2$ a corresponding equation, *viz.*, $R_2 = M_2[(v_1 + b)(n_1^2 - 1)/(n_1^2 + 2) + 3v_1\gamma n_1^2/(n_1^2 + 2)^2]$, for the molecular refraction, whereupon the full $_{\infty}(_{O}P_2)$ is seen to exceed that from Smith's

* Subscripts 1 and 2 refer to solvent and solute respectively. This is the reverse of the convention followed by Le Fèvre for many years (cf. *J.*, 1952, 1932). A solution is denoted by the subscript 12.

expression by the extra term $3M_2(v_1 + b)(\varepsilon_1 - n_1^2)/(\varepsilon_1 + 2)(n_1^2 + 2)$. This is negligible when ε_1 and n_1^2 are nearly equal and M_2 not too great, but if b {*i.e.*, $[(v_{12} - v_1)/w_2]_{w_2=0}$} is large, or $\alpha\varepsilon_1$ of the same order as γn_1^2, results may be disappointing. Two numerical applications are discussed later.

The primary motive for the present work arose from the matters listed at the outset under (*b*). Buckingham and Le Fèvre (*loc. cit.*) recorded polarity measurements for thirteen compounds, chosen for their range of molecular shapes, to guide the selection of the best relation with which to connect $\mu_{solution}$ with μ_{gas}. On the whole the greatest success was achieved with the larger molecules. Published figures for small molecules as vapours and as solutions are sparse; usually only μ_{gas} is available, and $\mu_{solution}$ is lacking. With dissolved gases dependable accuracy is difficult to ensure, as experience with carbon suboxide, carbonyl chloride (*J.*, 1935, 1696), methylamine, etc. (*Trans. Faraday Soc.*, 1947, **43**, 374), sulphur dioxide (*J.*, 1950, 276), methyl chloride (*J.*, 1950, 556), ethylene oxide (*J.*, 1950, 3370), keten (*J.*, 1951, 2583), dimethyl ether (*J.*, 1952, 1643), hydrogen sulphide (*J.*, 1952, 1651), etc., has shown. We therefore decided to examine furan and thiophen since both these are ordinarily *liquid* and have had their structures metrically described (cf. Allen and Sutton, *Acta Cryst.*, 1950, **3**, 46). Moreover, their low dipole moments made them suitable for illustrating the points raised under (*a*).

Experimental

Furan, prepared as in *Org. Synth.* (Coll. Vol. I, 1941, p. 274), was dried (Na) and distilled immediately before use; it had b. p. 32°/760 mm. Thiophen, supplied by the Socony-Vacuum Oil Co., U.S.A., was dried (Na) and fractionated; the portion collected had b. p. 84·0°/761·4 mm. The benzene used as solvent was " crystallisable " grade which had been refluxed over aluminium chloride for some hours, washed several times with sulphuric acid followed by water, then dried (Na) and distilled. The product was partially frozen in contact with sodium wire and the fully solid portion remaining after decantation allowed to remelt.

The polarisations of furan and thiophen as gases were measured relatively to carbon dioxide with the apparatus and procedure described in *J.*, 1950, 290. Data are presented in Table 1,

Table 1. *Polarisation–temperature relations for furan and thiophen as gases.*

		Pressure range						Pressure range			
T, °K	No. of obs.	(cm. Hg)	x/x'	P (obs.)	P (calc.) *	T, °K	No. of obs.	(cm. Hg)	x/x'	P (obs.)	P (calc.) †
		Furan						Thiophen			
329	17	16—60	3·987	29·27	29·30	295	9	2—7	4·106	30·14	30·17
340	15	14—52	3·952	29·01	28·98	353	14	14—41	3·982	29·23	29·13
351	10	13—46	3·895	28·59	28·69	373	12	26—49	3·964	29·10	28·85
373	13	13—57	3·849	28·26	28·15	390	16	11—46	3·891	28·56	28·63
390	16	15—47	3·796	27·87	27·78	405	16	12—44	3·883	28·50	28·45
430	14	12—51	3·670	26·94	27·03	411	12	14—51	3·813	27·99	28·38
						431	14	11—48	3·849	28·26	28·17

* From equation : $P = 19{\cdot}63 + 3180/T$. † From equation : $P = 23{\cdot}83 + 1871/T$.

[The calibration equation used for both the above sets was $(\delta C/p)_{CO_2} = -0{\cdot}054 + 2307{\cdot}4/T$.]

the headings of which are self-explanatory except for x/x' which is the *observed* ratio $(\delta C/p)^{gas}_{p=0}/(\delta C/p)^{CO_2}_{p=0}$, whence P_{gas} follows as xP_{CO_2}/x'.

Dielectric constants (ε), densities (d), and refractive indices (n_D) for each of the solutes at various concentrations expressed as weight fractions (w) in benzene at 25° are recorded in Table 2. They were determined by standard techniques (cf. *J.*, 1948, 1949; 1949, **333**; " Dipole Moments," Methuen, 1948, Chap. II).

Calculation of Results.—The equations of the form $P = A + B/T$ shown in Table 1 were computed by the method of least squares. If $P_{obs.}$ minus $P_{calc.}$ is Δ, and n the number of temperatures studied, the standard errors in the A and B terms are given by $\pm s\{[\Sigma(1/T)^2]/D\}^{\frac{1}{2}}$ and $\pm s(n/D)^{\frac{1}{2}}$, respectively, where $s = [(\Sigma\Delta^2)/(n-2)]^{\frac{1}{2}}$ and $D = n\Sigma(1/T)^2 - [\Sigma(1/T)]^2$ (cf. Youden, *Analyt. Chem.*, 1947, **19**, 946). Inserting appropriate values, we have

for furan : $P = (19{\cdot}63 \pm 0{\cdot}47) + (3180 \pm 170)/T$ whence $\mu = 0{\cdot}72 \pm 0{\cdot}02$D

for thiophen : $P = (23{\cdot}83 \pm 0{\cdot}67) + (1871 \pm 249)/T$ whence $\mu = 0{\cdot}55 \pm 0{\cdot}04$D

The measurements listed in Table 2 have been utilised to test the three extrapolation procedures used here for several years. All are based on the proposals made by Le Fèvre and Vine (*J.*, 1937, 1805) and require estimates of the two "constants" α or β (p. 1622); these may be

TABLE 2. *Dielectric constants, densities, etc., for furan and thiophen in benzene at 25°.*

Furan

10^5w_2	ε	d	n_D	10^5w_2	ε	d	n_D	10^5w_2	ε	d	n_D
0	2·2725	0·87378	1·4976	4425	2·3003	0·87596	1·4940	7995·5	2·3208	0·87774	—
1709·5	2·2833	0·87469	—	5622·5	2·3077	0·87659	—	8276	—	—	1·4911
3565	2·2948	0·87562	—	5935	2·3090	0·87679	—	8510·5	2·3231	0·87803	—
3702	2·2956	0·87567	—	5935·5	2·3090	0·87678	1·4930	8995	—	—	1·4907
4397·5	2·2990	0·87601	—								

Thiophen

10^5w_2	ε	d	n_D	10^5w_2	ε	d	n_D	10^5w_2	ε	d	n_D
0	2·2725	0·87378	1·4976	2459	—	0·87769	—	5403	—	0·88225	—
634	2·2754	0·87481	—	3088	2·2820	0·87806	1·4980	5874	2·2909	0·88250	—
1318·5	2·2777	0·87587	—	3758	—	0·87970	—	6994	2·2947	0·88452	—
1673	2·2783	0·87685	—	4312	2·2876	—	—	8890	—	—	1·4992
1962	2·2802	—	—	4960	—	—	1·4985				

obtained by averaging expressions (1), (2), (7), and (8), fitting a straight line to the apparent values of $\alpha\varepsilon_1$ or βd_1 at each w_2 [expressions (3), (4), (9), (10)], or assuming that $\delta\varepsilon = \varepsilon_{12} - \varepsilon_1$ and $\delta d = d_{12} - d_1$ are related to w_2 by a power series [expressions (5), (6), (11), (12)]. Thus from Table 2 we derive for furan :

$$\Sigma(\varepsilon_{12} - \varepsilon_1)/\Sigma(w_2) = 0{\cdot}613 \quad . \quad . \quad . \quad (1)$$

$$\Sigma(d_{12} - d_1)/\Sigma(w_2) = 0{\cdot}0503_5 \quad . \quad . \quad . \quad (2)$$

$$(\alpha\varepsilon_1)_{w_2} = 0{\cdot}641_5 - 0{\cdot}48w_2 \quad . \quad . \quad . \quad (3)$$

$$(\beta d_1)_{w_2} = 0{\cdot}0528 - 0{\cdot}042w_2 \quad . \quad . \quad (4)$$

$$\delta\varepsilon = 0{\cdot}646w_2 - 0{\cdot}57w_2^2 \quad . \quad . \quad . \quad (5)$$

$$\delta d = 0{\cdot}0517w_2 - 0{\cdot}024w_2^2 \quad . \quad . \quad . \quad (6)$$

and for thiophen :

$$\Sigma(\varepsilon_{12} - \varepsilon_1)/\Sigma(w_2) = 0{\cdot}336 \quad . \quad . \quad . \quad (7)$$

$$\Sigma(d_{12} - d_1)/\Sigma(w_2) = 0{\cdot}154_5 \quad . \quad . \quad . \quad (8)$$

$$(\alpha\varepsilon_1)_{w_2} = 0{\cdot}415 - 1{\cdot}71w_2 \quad . \quad . \quad . \quad (9)$$

$$(\beta d_1)_{w_2} = 0{\cdot}166 - 0{\cdot}231 \quad . \quad . \quad . \quad (10)$$

$$\delta\varepsilon = 0{\cdot}373w_2 - 0{\cdot}86w_2^2 \quad . \quad . \quad . \quad (11)$$

$$\delta d = 0{\cdot}156w_2 - 0{\cdot}042_5w_2^2 \quad . \quad . \quad . \quad (12)$$

We have used all the above to calculate $\delta\varepsilon$ and δd and find that the sums, for each equation, of the squares of the differences from the observed values run in descending orders as follow :

for furan $\begin{cases} \delta\varepsilon \ . \ . \ . \ (1) > (3) = (5) \\ \delta d \ . \ . \ . \ (2) > (4) > (6) \end{cases}$ for thiophen $\begin{cases} \delta\varepsilon \ . \ . \ (7) > (9) > (11) \\ \delta d \ . \ . \ (8) \doteqdot (10) > (12) \end{cases}$

Similar surveys, *e.g.*, on the solutions discussed in *Trans. Faraday Soc.*, 1950, **46**, 1, have shown the same sequences. Accordingly, we propose in future to replace forms such as (3) or (4) by (5) or (6) whenever ε_{12} or d_{12} measurements are clearly seen not to be rectilinear with w_2. This amends the practice recommended in the paper just cited.

In such cases it will be of interest therefore to assess the standard error of the constant α in a regression of the type $\delta Q = aw_2 + bw_2^2$. If Δ is the difference between $(\delta Q)_{obs.}$ and $(\delta Q)_{calc.}$, the desired standard error is $\pm\,[(\Sigma\Delta^2)/(\text{degrees of freedom})\ \Sigma(w_2 - \bar{w}_2)^2]^{\frac{1}{2}}$.

Thus $\alpha\varepsilon_1$ and βd_1 at $w_2 = 0$ become, from Table 2,

$$\text{for furan : } \alpha\varepsilon_1 = 0{\cdot}646 \pm 0{\cdot}008;\ \beta d_1 = 0{\cdot}0517 \pm 0{\cdot}0006$$

$$\text{for thiophen : } \alpha\varepsilon_1 = 0{\cdot}373 \pm 0{\cdot}013;\ \beta d_1 = 0{\cdot}156 \pm 0{\cdot}005$$

whence, using ${}_\infty P_2 = p_1\,(1 - \beta) + C\alpha\varepsilon_1$, and multiplying by M_2, we find ${}_\infty P_2$ to be $30{\cdot}10 \pm 0{\cdot}12$ c.c. for furan or $29{\cdot}45 \pm 0{\cdot}34$ c.c. for thiophen.

Using the distortion polarisations reported above (*viz.*, $19{\cdot}63 \pm 0{\cdot}47$ and $23{\cdot}83 \pm 0{\cdot}67$ c.c., respectively), we obtain the apparent moments in benzene of these solutes as :

$$\text{furan : } \mu = 0{\cdot}71_5 \pm 0{\cdot}02\ \text{D} \qquad \text{thiophen : } \mu = 0{\cdot}52 \pm 0{\cdot}05\ \text{D}$$

We now refer to the approximate calculation of orientation polarisations by routes which avoid d_{12} determinations (see p. 1622). Knowledge of $(n_{12}^2 - n_1^2)/w_2$ for $w_2 = 0$ is required; since usually the refractive index of a solution obeys the equation $n_{12}^2 = n_1^2(1 + \gamma w_2)$, a mean value of γn_1^2 can be obtained as $\Sigma(n_{12}^2 - n_1^2)/\Sigma w_2$. From Table 2 this magnitude is $-0{\cdot}234$ for furan and $+0{\cdot}0514$ for thiophen. As a check on these, R_2 may be computed as M_2r_2 *via*

$${}_\infty r_2 = r_1(1 - \beta) + G\gamma n_1^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (a)$$

where $G = 3/d_1(n_1^2 + 2)^2 = 0{\cdot}1907$, and $r_1 = 0{\cdot}3352$ c.c. The molecular refractions thus derived (18·4 and 24·0 c.c.) are close to those (18·4 for α line, 24·3 for D line) listed in Landolt–Börnstein's " Tabellen." If equation (*a*) is subtracted from Le Fèvre and Vine's equation (*b*)

$$_{\infty}P_2 = p_1(1 - \beta) + C\alpha\varepsilon_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (b)$$

the specific orientation polarisation at infinite dilution follows as :

$$_{\infty}(_0P_2) = \frac{3(1 - \beta)(\varepsilon_1 - n_1^2)}{d_1(\varepsilon_1 + 2)(n_1^2 + 2)} + \frac{3}{d_1}\left[\frac{\alpha\varepsilon_1}{(\varepsilon_1 + 2)^2} - \frac{\gamma n_1^2}{(n_1^2 + 2)^2}\right] \quad . \quad . \quad . \quad . \quad . \quad (c)$$

These terms are equivalent to those quoted on p. 1622, but are more suitable for the insertion of quantities already recorded in this paper. Smith's suggestion (*loc. cit.*) is to omit the left-hand member of (*c*).

Substitution of the appropriate values of β, $\alpha\varepsilon_1$, etc., shows that (*c*) is, for furan $_{\infty}(_0P_2) = 0{\cdot}005 + 0{\cdot}166$ c.c., and for thiophen $_{\infty}(_0P_2) = 0{\cdot}005 + 0{\cdot}060$ c.c.

Smith's proposal therefore neglects terms which are *ca.* 3 or 8% respectively of the apparent orientation polarisations deducible by the normal " refractivity " method. Guggenheim's approximation (*loc. cit.*), that $_{\infty}(_0P_2) = 3(\alpha\varepsilon_1 - \gamma n_1^2)/d_1(\varepsilon_1 + 2)^2$, applied to the present examples yields values ($0{\cdot}165_5$ and $0{\cdot}060_5$ c.c.) which are close to those by Smith's procedure. However, despite the percentage errors just mentioned, the moments (*viz.*, 0·7 and 0·5 D) estimated *via* these " short-cut " routes compare satisfactorily with the values $0{\cdot}71_5 \pm 0{\cdot}02$ and $0{\cdot}52 \pm 0{\cdot}05$ D recorded above.

Discussion

Comparison with Earlier Determinations.—Moments previously reported for furan and thiophen are included in Table 3 (measurements in solution being indicated by the formula of the solvent).

Table 3. *Recorded dipole moments of furan and thiophen.*

μ, D	How determined	Reference
	Furan	
0·63	C_6H_6	Hunter and Partington, *J.*, 1931, 2062
0·71	C_6H_6	Smyth and Walls, *J. Amer. Chem. Soc.*, 1932, **54**, 3230
0·67 ± 0·02	C_6H_6	Robles, *Rec. Trav. chim.*, 1939, **58**, 111
0·661 ± 0·006	Stark splitting	Sirvetz, *J. Chem. Phys.*, 1951, **19**, 1609
0·72 ± 0·02	Gas	Present paper
$0{\cdot}71_5$ ± 0·02	C_6H_6	" "
	Thiophen	
0·63	Solvent unstated	Hassel and Naeshagen, *Tids. Kjemi Berg.*, 1930, **10**, 31
0·53	C_6H_6	Higasi, *Bull. Inst. Phys. Chem. Res. Tokyo*, 1932, **11**, 729
0·54	C_6H_{14}	
0·58	Gas	Kubo, *Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1936, **29**, 122
0·54 ± 0·02	C_6H_6	Robles, *loc. cit.*
0·53	C_6H_6	Keswani and Freiser, *J. Amer. Chem. Soc.*, 1949, **71**, 218
0·55 ± 0·04	Gas	Present paper
0·52 ± 0·05	C_6H_6	" "

The Ratios $\mu_{solution}/\mu_{gas}$.—These are seen to be, from experiment, 0·99 ± 0·06 for furan and $0{\cdot}94_5 \pm 0{\cdot}16$ for thiophen; they will now be compared with predictions by Buckingham and Le Fèvre's equations nos. (1), (2), and (4) (*loc. cit.*).

Necessary data—other than those already quoted in this paper—are the following: From scale drawings, using the dimensions listed by Allen and Sutton (*Acta Cryst.*, 1950, **3**, 46), upon which " Wirkungsradien " are superposed, we derive :

	A	*B*	*C*	Exp x^2	ξ
Furan	5·10	6·11	2·90	0·624	0·28
Thiophen	5·82	6·44	3·08	0·555	0·26

The internal field functions ξ are evaluated from A/B and C/B more conveniently by using Osborn's tables of demagnetising factors (cf. *Phys. Review*, 1945, **67**, 351) than the small diagram originally published by Ross and Sack (*Proc. Phys. Soc.*, 1950, **63**, 893). The refractive indices of the two solutes at 25° (Na light) are 1·4186 and 1·5270, respectively.

Substitution gives $\mu_{C_4H_4}/\mu_{gas}$ by the various equations as follows:

	By eqn. (1)	By eqn. (2)	By eqn. (4)	By expt.
Furan	0·92	0·93	0·93	$0·99 \pm 0·06$
Thiophen	0·94	0·94	0·94	$0·94_5 \pm 0·16$

The situation with thiophen is satisfactory; it is less so with furan. However, in both cases all equations give the correct qualitative forecast—that μ_{gas} exceeds $\mu_{C_4H_4}$.

The Ratios μ_{liquid}/μ_{gas}.—The dielectric constant of liquid furan, measured relatively to benzene at 25°, is 2·942, its density is 0·9313 g./c.c., whence ${}_TP_{liquid} = 28·72$ c.c. and $\mu_{liquid} = 0·67$ D. Buckingham and Le Fèvre's equation (5) requires μ_{liquid}/μ_{gas} to be 0·87, but the value found is 0·93. For thiophen we have $\varepsilon_{25} = 2·705$, $d_4^{25} = 1·0583$, and ${}_TP_{liquid} = 28·81$ c.c., so $\mu_{liquid} = 0·49$ D and $\mu_{liquid}/\mu_{gas} = 0·89$; equation (5) predicts this ratio as 0·89 also.

Thus from ε, d, and n_D observations on the pure materials we should expect μ_{gas} to be 0·77 and 0·55 D, respectively. Incorrect as is the former figure, it is a better estimate of μ_{gas} than that produced by Onsager's equation (No. 7 in Buckingham and Le Fèvre, *loc. cit.*), which with the data used here leads to 0·42 D for furan and 0·46 D for thiophen.

Atomic Polarisations.—Using the molecular refractions listed by Landolt-Börnstein ("Tabellen, 4th edn., p. 1029) for various wave-lengths, Kubo (*loc. cit.*) calculated R_∞ for thiophen as 22·7 c.c.; from the same source we now obtain 17·9 c.c. for furan. From the P–$1/T$ relations given above, atomic polarisations of furan and thiophen follow as $1·7 \pm 0·5$ and $1·1 \pm 0·7$ c.c. (or about 10 and 5% of R_∞), respectively. With diethyl ether and sulphide the magnitudes stand in the same order (*viz.*, *ca.* 2·5 and 1·6 c.c.—figures which are *ca.* 11 and 6% of the corresponding electronic polarisations; cf. Barclay and Le Fèvre, *J.*, 1952, **1643**; Kubo, *loc. cit.*).

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327. *The Dipole Moment of Pyrrole measured in the Dissolved and in the Gaseous State.*

By A. D. BUCKINGHAM, B. HARRIS, and R. J. W. LE FÈVRE.

The apparent dipole moment of pyrrole dissolved in benzene is slightly lower than that as a gas. Such a relationship is qualitatively predicted by equations (1) and (2) of Buckingham and Le Fèvre (*J.*, 1952, 1932).

IT is well known that small dipole moments are difficult to determine with accuracy. Hence the numerical quotients $\mu_{solution}/\mu_{gas}$, obtained by dividing values from experiment, are likely to be more certain the larger the polarity of the molecule considered. From this viewpoint, pyrrole ($\mu = ca.$ 1·8 D) should be a better compound to study than either furan ($\mu = ca.$ 0·7 D) or thiophen ($\mu = 0·5$ D) (see preceding paper). An examination of this base is therefore now reported.

Present Work.—Pyrrole was obtained by heating ammonium mucate (cf. *Org. Synth.*, Coll. Vol. 1, 1941, p. 473); it was redistilled over potassium hydroxide before use.

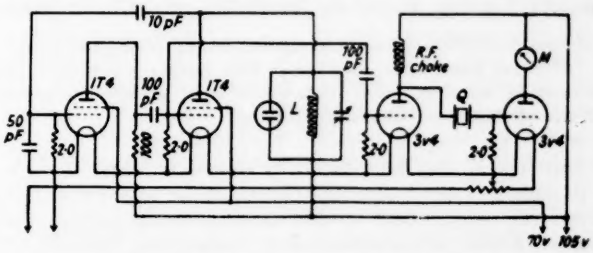
Polarisations of vaporised pyrrole at five temperatures were recorded relatively to carbon dioxide. Essential readings are in Table 1.

TABLE 1. *Polarisation–temperature relation for gaseous pyrrole.*

T, °K	No. of obs.	Press. range (cm. Hg)	x/x'	P (obs.)	P (calc.) *	T, °K	No. of obs.	Press. range (cm. Hg)	x/x'	P (obs.)	P (calc.) *
391·3	9	3—10	$10·03_5$	73·67	73·58	452·0	7	9—20	$9·19_4$	67·49	66·48
413·8	11	9—19	$9·59_5$	70·44	70·71	465·7	9	10—28	$8·78_1$	64·46	65·13
426·9	10	7—16	$9·39_5$	68·97	69·16						

* Calibrating equation used: $(\delta C/p)_{CO_2} = -0·157 + 2229·5/T$.

The dielectric constants of solutions of pyrrole in benzene were determined with a circuit newly constructed to replace that used previously (cf. *J.*, 1948, 1949), which suffered from " drifts " as the batteries gradually became discharged. Details are shown in the Figure. Only miniature valves are employed so that a conventional power-pack, stabilised by voltage-regulator



tubes, is sufficient to provide both heater current and high-tension supply. The (Franklin) oscillator, with its filaments connected in series, is followed by a " buffer " R.F. amplifier, which in turn is coupled through a mounted quartz-crystal-containing condenser to a valve voltmeter. The dielectric cell and standard variable capacity are joined in parallel across the inductance L. The reference point is taken as the centre of the sigmoid curve exhibited by M as the oscillation frequency passes through the natural frequency of the quartz crystal. Measurements obtained, and equations fitted thereto by the method of least squares, are given in Table 2. Quoting standard errors, we find from Table 1: $(P)_T = (20{\cdot}8 \pm 5{\cdot}2) + (20{,}636 \pm 2232)/T$, whence $\mu_{gas} = 1{\cdot}84 \pm 0{\cdot}08$ D; and from Table 2: $(\alpha\varepsilon_1)_{w_1=0} = 5{\cdot}282 \pm 0{\cdot}014$, and $(\beta d_1)_{w_1=0} = 0{\cdot}0947 \pm 0{\cdot}0001$, so that $_\infty P_2$ becomes $87{\cdot}04 \pm 0{\cdot}17$ c.c. With a distortion polarisation of $20{\cdot}8 \pm 5{\cdot}2$ c.c., the dipole moment of pyrrole in benzene follows as $1{\cdot}80 \pm 0{\cdot}07$ D. These results are in harmony with others in the literature (see Table 3).

TABLE 2. *Pyrrole in benzene at 25°.*

$10^6 w_2$	0	12,450	26,350	31,635	36,748
ε_{25}	2·2725	2·3385	2·4146	2·4440	2·4711
d_4^{25}	0·87378	0·87493	0·87614	0·87654	0·87697

whence $\delta\varepsilon = (\varepsilon_{12} - \varepsilon_1)_{w_2} = 5{\cdot}282\, w_2 + 3{\cdot}8\, w_2^2$

and $\delta d = (d_{12} - d_1)_{w_2} = 0{\cdot}0947\, w_2 - 0{\cdot}22\, w_2^2$

$10^4\delta\varepsilon$ (obs.)	660	1421	1715	1986
,, (calc.)	663	1418	1709	1992
$10^5\delta d$ (obs.)	115	236	276	319
,, (calc.)	115	234	277	318

TABLE 3. *Dipole-moment values recorded for pyrrole.*

Moment, D	Method	Authors
1·80 ± 0·07	In benzene at 25°	This paper.
1·84 ± 0·08	Gas	,, ,,
1·80	In benzene at 25°	Kofod, Sutton, and Jackson, *J.*, 1952, 1467.
1·80	,, ,, 20°	Robles, *Rec. Trav. chim.*, 1939, **58**, 111.
1·83	,, ,, ,,	Cowley and Partington, *J.*, 1933, 1259.

Predicted Values of $\mu_{solution}/\mu_{gas}$.—Scale drawings based on the dimensions of the pyrrole molecule quoted by Allen and Sutton (*Acta Cryst.*, 1950, **3**, 46), together with Stuart's " Wirkungsradien," give—if the N–H bond is taken as lying in the C_4-plane—$A = 5{\cdot}83_5$, $B = 6{\cdot}12$, and $C = 2{\cdot}90$, whence $\exp x^2 = 0{\cdot}504_5$. For the Na-D line $n^{25}_{pyrrole}$ is 1·5051 and $n^{25}_{benzene}$ is 1·4976. The volume polarisation of benzene at 25° is 0·2978. Accordingly, we would predict the ratio $\mu_{C_6H_6}/\mu_{gas}$ as $0{\cdot}92_3$ or 0·93 respectively by the equations (1) or (2) of *J.*, 1952, 1932. The value now found is $0{\cdot}98 \pm 0{\cdot}08$. The Ross–Sack equation [*i.e.* (4) in the same paper] forecasts 0·92 (using a ξ factor of 0·24, cf. Osborn, *Phys. Review*, 1945, **67**, 351). All three relations, therefore, correctly require the " solvent effect " (*viz.*, $\pm\delta\mu = \mu_{soln.} - \mu_{gas}$) to be negative in sign, in accordance with experiment. As with furan, however, the *observed* $-\delta\mu$ is somewhat smaller than that calculated. Remembering the uncertainties underlying the " Wirkungsradien " used to produce A, B, and C, we view the result, on the whole, as satisfactory.

UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA. [*Received, December 10th*, 1952.]

328. *The Chemistry of Reductone. Part III.* Alkenediols related to Reductone.*

By Wesley Cocker, David S. Jenkinson, and Peter Schwarz.

The anilino- and *N*-methylanilino-derivatives of phenylreductone (I*a–b*; R = Ph, R′ = H) have been prepared. The parent compound has been obtained only in solution. The ultra-violet light absorption spectra and the stabilities of these compounds are discussed.

Alkenediols of type (I*a–b*) may be difficult to isolate for three main reasons. In the first place, they can undergo rapid tautomeric change to the appropriate hydroxydicarbonyl compounds of type (II) (*e.g.*, ethyl αβ-dihydroxycrotonate yields ethyl α-hydroxy-β-ketobutyrate; Karrer, Kebrle, and Thakkar, *Helv. Chim. Acta*, 1950, **33**, 1711). Secondly, they may be transformed into esters of type (III), a change which is catalysed by hydroxyl ions; *e.g.*, (I; R = R′ = Ph) yields benzoyloxyacetophenone (III; R = R′ = Ph) (Karrer *et al.*, *loc. cit.*). And, thirdly, they may undergo oxidation in air.

R·C(OH):C(OH)·COR′ ⇌ R·CO·C(OH):CR′·OH R·CO·CH(OH)·COR′ R·CO·CH_2·O·COR′
(I*a*) (I*b*) (II) (III)

RR′CH·CO·COR″ Ph·CO·C(OH):CH·NRPh PhRN·CH:C(OH)·CHO
(IV) (V) (VI)

Arndt, Loewe, and Ayça (*Chem. Ber.*, 1951, **84**, 333) have discussed some of the structural factors which can influence resistance to ketonisation and oxidation. In order to obtain information on these points we had previously set out to prepare αβ-dihydroxy-β-phenylacraldehyde (I*a*; R = Ph, R′ = H), hereafter called phenylreductone, and mesitylreductone (I; R = mesityl, R′ = H). Neither of these compounds was obtained as a stable solid; aqueous solutions of the former were, however, obtained.

Hydrolysis of 3-bromo-1-phenylpropane-1 : 2-dione (IV; R = H, R′ = Br, R″ = Ph) with barium hydroxide gave a barium salt with properties similar to those of an ene-diol, but phenylreductone could not be isolated from the salt; nor could phenylreductone be obtained by hydrolysis of the bromo-compound with sulphuric acid, although Hesse and Bucking (*Annalen*, 1949, **563**, 31) obtained a stable ene-diol from 3-chloro*cyclo*pentane-1 : 2-dione in this way.

3-Acetoxy-1-phenylpropane-1 : 2-dione (IV; R = H, R′ = OAc, R″ = Ph) was obtained in small yield by reaction of either the above bromo-diketone with acetic anhydride and sodium acetate, or lead tetra-acetate with 1-phenylpropane-1 : 2-dione (IV; R = R′ = H, R″ = Ph), benzoic acid being a by-product in the latter reaction. The acetoxy-compound fails to give a ferric reaction, whereas the related compound (IV; R = OAc, R′ = Ph, R″ = mesityl), enolises completely when its solution is kept (Barnes and Green, *J. Amer. Chem. Soc.*, 1938, **60**, 1549). Acid hydrolysis of the acetoxy-compound yielded a solution which gave colour and reducing reactions of an ene-diol, and iodine titrations indicated the production of an ene-diol, presumably phenylreductone, in theoretical quantity. It was not possible to isolate pure phenylreductone from the solution; kept under nitrogen, the solution was stable, although oxidation took place rapidly in air.

Anilino- and *N*-methylanilino-analogues of phenylreductone (V; R = H and Me, respectively) were readily obtained by reaction of 3-bromo-1-phenylpropane-1 : 2-dione with aniline and methylaniline, respectively. Both analogues gave a green ferric colour, exhibited complete enolisation towards iodine, and decolorised two equivalents of Tillmans's reagent in presence of mineral acid. Their ene-diol-like character steadily deteriorated when aqueous-alcoholic solutions were exposed to air. Whilst the anilino-compound gave Fearon and Kawerau's ene-diol (*o*-dinitrobenzene) reaction (*Biochem. J.*, 1943, **37**, 326), the methylanilino-compound gave no immediate colour, thus resembling the corre-

* Part II, *J.*, 1950, 2052.

sponding analogues of reductone (VI; R = H and Me, respectively) (cf. Cocker, O'Meara, Schwarz, and Stuart, *J.*, **1950**, 2052).

The ultra-violet light absorption characteristics of (V; R = H and Me) resemble each other (cf. the corresponding reductone derivatives; Cocker *et al.*, *loc. cit.*), and also those of 3-anilino-1-phenylprop-2-en-1-one (Bowden, Braude, Jones, and Weedon, *J.*, **1946**, 45). The spectra of alcoholic solutions of (V; R = H and Me) change with time, but solutions in *cyclo*hexane are unaffected. The rate of change is very slow when a solution of (V; R = H), in alcohol saturated with nitrogen, is kept under nitrogen. In the reductone series, (VI; R = H) but not (VI; R = Me) undergoes a similar change. After long storage in alcoholic solution (V; R = H or Me) and (VI; R = H) show similar spectral characteristics. The change is probably due to oxidation (cf. Cocker *et al.*, *loc. cit.*).

Light absorption data.

	In *cyclo*hexane		In alcohol	
	$\lambda_{max.}$ (Å)	log ε	$\lambda_{max.}$ (Å)	log ε
(V; R = H)	2390	4·06	* 2420	4·06
	2650	3·93	* 3680	4·44
	3620	4·41	† 2350	4·23
(V; R = Me)	2410	4·04	* 2430	4·05
	2690	3·86	* 3670	4·36
	3660	4·37	‡ 2330	4·18
PhCO·CH:CH·NHPh	—	—	2420, 2540	4·24
			3740	4·49

* Observation 20 min. after dissolution. † After 40 hr. ‡ After 48 hr.

Attempts to prepare mesitylreductone were unsuccessful. 1-Mesitylpropane-1 : 2-dione 2-oxime, prepared by the nitrosation of 1-mesitylpropan-1-one, was hydrolysed to 1-mesitylpropane-1 : 2-dione (cf. *Org. Synth.*, 1936, **16**, 44; 1943, **23**, 1). The latter could not be successfully brominated; nor was it acetoxylated with lead tetra-acetate. We were unable to prepare 2 : 3-diketo-3-phenyl- and -3-mesityl-propaldehyde (which could possibly be reduced to phenyl- and mesityl-reductone, respectively) by the oxidation of 1-phenyl- and 1-mesityl-propane-1 : 2-dione with selenium dioxide, although in the latter case the oily product yielded a compound, probably 2-mesitylquinoxaline, with *o*-phenylenediamine. 1-Mesitylpropane-1 : 2-dione did not give a quinoxaline (Fuson and Soper, *J. Org. Chem.*, 1944, **9**, 123).

The stability of the enol forms of phenylreductone and of its anilino-derivative under nitrogen indicates that, like reductone and its anilino-derivatives, these compounds do not ketonise spontaneously. However, the two series of compounds differ appreciably in their stability towards oxidation, phenylreductone and its derivatives being the more readily oxidised.

Experimental

Hydrolysis of 3-*Bromo*-1-*phenylpropane*-1 : 2-*dione* (IV; R = H, R′ = Br, R″ = Ph).—The bromo-compound (0·4 g.) was added to an ice-cold saturated solution of barium hydroxide (15 c.c.) under nitrogen. After 10 min., the golden-yellow precipitate (0·1 g.) of barium salt was collected and washed with ether. Dissolved in dilute acetic acid, this consumed 51·5% of the amount of N/10-iodine expected for the barium salt of phenylreductone.

3-*Acetoxy*-1-*phenylpropane*-1 : 2-*dione* (IV; R = H, R′ = OAc, R″ = Ph).—(a) *From* 3-*bromo*-1-*phenylpropane*-1 : 2-*dione*. A mixture of bromo-compound (1·3 g.), freshly fused and powdered sodium acetate (1·0 g.), and acetic anhydride (5 c.c.) was refluxed for 15 min. The dark brown product was poured into water and extracted with chloroform, and the extracts were washed repeatedly with water. After evaporation of the solvent, the main fraction distilled at 175—185°/12 mm. and partly solidified when rubbed and cooled. The *acetate* (0·07 g.) was separated and crystallised (charcoal) from light petroleum containing 1 drop of alcohol, giving plates, m. p. 88—89° (Found: C, 63·5; H, 5·4. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%). It was slowly soluble in 20% aqueous sodium hydroxide; after a few min., the solution gave a strong ene-diol colour reaction.

(b) *From* 1-*phenylpropane*-1 : 2-*dione*. A mixture of this compound (7·4 g.), freshly recrystallised lead tetra-acetate (22·5 g.), and glacial acetic acid (20 g.) was heated carefully to 100°. A vigorous reaction set in and the temperature was kept at 99—102° by cooling. After 10 min. the tetra-acetate had dissolved and after a further 5 min. the mixture had become brown. It was poured into water and extracted with ether, and the extract thoroughly shaken with 5% aqueous sodium hydrogen carbonate. The dried ethereal extract was distilled, leaving a brown oil (3·3 g.) which partly solidified (0·42 g.) at 0°. Crystallised from light petroleum–ethyl acetate, it did not depress the m. p. of a specimen of the acetate prepared by method (a).

Attempted Isolation of Phenylreductone (I; R = Ph, R′ = H).—Powdered 3-acetoxy-1-phenylpropane-1 : 2-dione (0·35 g.) was stirred with concentrated sulphuric acid (11 g.) for 15 min. at −5°. The acetate slowly dissolved, giving a pale orange solution which was poured on ice under nitrogen (total volume after melting, 33·0 c.c.; 1 c.c. of this solution decolorised 10·2 c.c. of N/100-iodine. Calc. for complete hydrolysis to phenylreductone = 10·3 c.c.). After being kept overnight under nitrogen, the aqueous solution showed no change in iodine titre, but when air was admitted the titre decreased rapidly. The product was extracted under nitrogen with chloroform, which was evaporated under reduced pressure at 0°, leaving a colourless oil which slowly crystallised. However, on admission of air the crystals gave an intractable oil.

3-*Anilino*-2-*hydroxy*-1-*phenylprop*-2-*en*-1-*one* (V; R = H).—3-Bromo-1-phenylpropane-1 : 2-dione (1·65 g.) and aniline (0·64 g.) were mixed, with cooling, and the resulting red gum was rubbed with light petroleum, giving a pale yellow hygroscopic hydrobromide (1·25 g.) which could not be purified. This was shaken with a mixture of chloroform and 5% sodium hydrogen carbonate solution, and the chloroform layer was washed with water, dried, and treated with charcoal. Addition of light petroleum yielded the required *anilino*-compound, which crystallised from chloroform–light petroleum as golden-yellow prisms, m. p. 135° (open tube), decomp. 173° (sealed tube) (Found : C, 75·0; H, 5·5. $C_{15}H_{13}O_2N$ requires C, 75·3; H, 5·4%).

2-*Hydroxy*-3-*N*-*methylanilino*-1-*phenylprop*-2-*en*-1-*one* (V; R = Me).—3-Bromo-1-phenylpropane-1 : 2-dione (3·3 g.) in ether (5 c.c.) was added to methylaniline (1·56 g.) in ether (10 c.c.). A pale yellow hydrobromide (3·4 g.) separated overnight. It was shaken with 5% sodium hydrogen carbonate solution and ether, and the ethereal solution was washed with water, dried, and evaporated. The remaining oil was dissolved in benzene (10 c.c.) and purified on an alumina column. Development with benzene gave three bands, the second of which was eluted with benzene containing 10% of alcohol, giving the *methylanilino*-compound (1·7 g.) as a yellow oil which solidified when rubbed. This crystallised from chloroform–light petroleum as yellow needles, m. p. 118·5° (sealed tube) (Found : C, 70·6; H, 5·6. $C_{16}H_{15}O_2N,H_2O$ requires C, 70·8; H, 6·3%). On recrystallisation from benzene–light petroleum, the water of crystallisation was lost (Found : C, 75·6; H, 6·7. $C_{16}H_{15}O_2N$ requires C, 75·9; H, 5·9%).

1-*Mesitylpropane*-1 : 2-*dione* 2-*Oxime*.—This (57·0 g.) was prepared from 1-mesitylpropan-1-one (62 g.) by the method described for oximinopropiophenone (*Org. Synth.*, 1936, **16**, 44). It crystallised from benzene–light petroleum as colourless plates, m. p. 123° (Found : C, 70·4; H, 7·6. $C_{12}H_{15}O_2N$ requires C, 70·3; H, 7·3%). Hydrolysis with sulphuric acid (*Org. Synth.*, 1943, **23**, 1) gave 1-mesitylpropane-1 : 2-dione (cf. Fuson and Soper, *loc. cit.*), b. p. 133—134°/14 mm. (Found : C, 75·6; H, 7·5. Calc. for $C_{12}H_{14}O_2$: C, 75·8; H, 7·4%).

Attempted Preparation of 2 : 3-*Diketo*-3-*mesitylpropaldehyde*.—The above diketone (1·9 g.) was refluxed for 2 hr. with selenium dioxide (1·0 g.) in dioxan (25 c.c.) and water (0·25 c.c.). The filtered solution was evaporated under reduced pressure, leaving an intractable gel (2·1 g.), which (0·42 g.) was refluxed with *o*-phenylenediamine (0·22 g.) in glacial acetic acid (6·0 c.c.). The cooled mixture was poured into 5% sodium hydrogen carbonate solution and extracted with ether, from which a brown oil (0·06 g.) was obtained. It slowly solidified, and was then crystallised from alcohol (charcoal) as colourless needles, m. p. 297·5° (Found : C, 77·1; H, 5·9. Calc. for $C_{18}H_{16}ON_2$: C, 78·3; H, 5·8%). It gave a blood-red colour with concentrated sulphuric acid.

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329. *The Hemicelluloses of Esparto Grass* (Stipa tenacissima, *L.*). *The Arabinose-rich Fraction.*

By G. O. Aspinall, E. L. Hirst, R. W. Moody, and (the late) E. G. V. Percival.

An arabinose-rich fraction has been isolated from esparto-grass hemicellulose. This gave on hydrolysis D-xylose (12 parts), L-arabinose (5 parts), D-glucose (1 part), and D-galactose (1 part). Hydrolysis of the methylated polysaccharide gave 2 : 3 : 5-trimethyl L-arabinose (1 part), 2 : 3-dimethyl D-xylose (3 parts), and 2-methyl D-xylose (1 part), together with smaller quantities of 2 : 3-dimethyl L-arabinose, 2 : 3 : 4 : 6-tetramethyl D-galactose, 2 : 4 : 6-trimethyl D-galactose, and 2 : 4-dimethyl D-galactose. It is concluded that the majority of the L-arabofuranose residues are present as side-chains attached to a main chain of 1 : 4-linked D-xylopyranose residues.

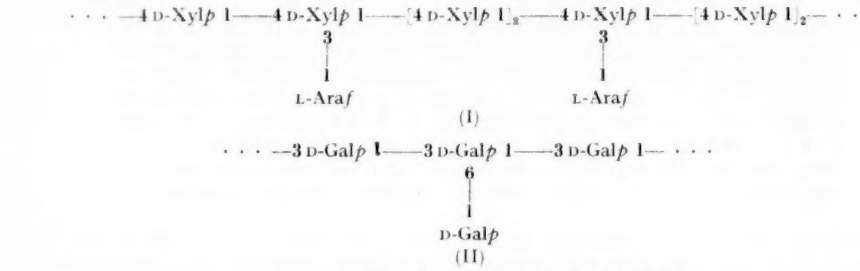
The presence of combined arabinose (*ca.* 7%) associated with esparto xylan has been known for some time and early work appeared to indicate that arabinose was present in the furanose form as an end group in a molecule comprising 18—20 xylopyranose residues (Haworth, Hirst, and Oliver, *J.*, 1934, 1917). More recently it was found that, by repeated fractional precipitation as the copper complex under carefully controlled and very mild conditions, a xylan devoid of arabinose residues could be obtained from esparto (Chanda, Hirst, Jones, and Percival, *J.*, 1950, 1289). This polysaccharide was shown to consist of a singly branched molecule containing 75(±5) D-xylopyranose units. These residues are linked through $C_{(1)}$ and $C_{(4)}$ except that the single branching point is formed by a 1 : 3-union. The mode of occurrence of the arabinose residues in the hemicellulose fraction remained obscure and the present investigation was undertaken to obtain fuller information on this point. Possibilities which could be envisaged were that the arabinose residues might be present in an associated araban of the type found in pectic substances (Hirst and Jones, *J.*, 1939, 452) or in a xyloaraban or araboxylan such as that recently isolated from wheat flour (Perlin, *Cereal Chem.*, 1951, **28**, 352). In the latter instance the arabofuranose residues were attached as side chains to a main chain of 1 : 4-linked D-xylopyranose units.

Crude esparto xylan was extracted from delignified esparto grass by the method of Chanda *et al.* (*loc. cit.*), and the hemicellulose thus obtained was extracted with hot 70% aqueous alcohol. This gave an arabinose-rich fraction, which on hydrolysis yielded xylose (12 parts), arabinose (5 parts), glucose (1 part), and galactose (1 part). Although many methods of extraction and fractionation were investigated the separation of an araban in a pure state was not achieved and we regard it as doubtful whether such a polysaccharide composed solely of arabinose residues does in fact occur in esparto hemicellulose.

The material richest in arabinose residues (hereinafter called polysaccharide A) was methylated, first by Fear and Menzies's method (*J.*, 1926, 937) and then with methyl iodide and silver oxide. The methylated derivative (OMe, 36·6%) was hydrolysed successively with methanolic and with aqueous hydrochloric acid, and the products of hydrolysis were chromatographed on a cellulose column. Although complete separation of all the fractions was not achieved, the presence of the following sugars was established by the isolation of crystalline derivatives (quantitative analyses indicated that these were present in the proportions shown in parentheses): 2 : 3 : 5-trimethyl L-arabinose (29), 2 : 3 : 4 : 6-tetramethyl D-galactose (4), 2 : 3-dimethyl D-xylose (100), 2 : 3-dimethyl L-arabinose (6), 2 : 4 : 6-trimethyl D-galactose (8), 2-methyl D-xylose (34), and 2 : 4-dimethyl D-galactose (8). The trimethyl pentose fraction was shown chromatographically to yield on demethylation a small quantity of xylose in addition to arabinose. It is likely therefore that the fraction contained, as is to be expected, a little 2 : 3 : 4-trimethyl xylose but attempts to form derivatives were unsuccessful. No methylated derivatives of glucose were isolated.

The small proportion of 2 : 3-dimethyl arabinose present together with the complete absence of a monomethyl arabinose preclude the existence of a multi-branched araban of

the type encountered in the pectic arabans. The proportions of the main constituents of the mixture of methylated sugars indicate that most of the arabofuranose residues must exist as side chains to a backbone of D-xylopyranose units, such side chains being attached to approximately every fourth xylose residue through position 3, as in (I). Owing to the incomplete methylation of the polysaccharide A it is impossible to ascribe definite structural



[For conventional symbols see *J.*, 1952, 5251.]

significance to the isolation of the small quantity of dimethyl arabinose. It is difficult also to account unambiguously for the methylated galactoses present. Although these residues could arise from a mixed polysaccharide, it is equally possible that a branched galactan exists as a separate entity, for which a possible repeating unit (II) is suggested above. The numerical results show, however, that many of the arabinose residues must have been attached to xylose residues and we conclude that there is present in the hemicellulose fraction of esparto an araboxylan of a type closely resembling the material discussed by Perlin (*loc. cit.*) and containing a main chain of 1 : 4-linked xylose residues to which L-arabofuranose residues are attached as side chains. The composition of this hemicellulose fraction is therefore extremely complex, much of the xylan being present, as previously shown by Chanda *et al.* (*loc. cit.*), as a true xylan containing no arabinose residues.

Experimental

Preparation of Polysaccharide A.—Crude esparto xylan was extracted from delignified esparto grass by the procedure of Chanda *et al.* (*loc. cit.*). The crude xylan (300 g.) was successively extracted four times for 24 hr. in batches (30 g.) with boiling aqueous alcohol (1 l.; 70% v/v), the insoluble material being removed by filtration of the hot extract. The filtrate was concentrated under diminished pressure, acidified with acetic acid, and poured into acetone (10 vols.). The collected precipitate (A) was washed successively with alcohol and ether and dried in a vacuum-desiccator (P_2O_5), to yield a fawn-coloured powder (35 g.; ash, 3·5%). Chromatographic examination of the hydrolysate (Hirst and Jones, *J.*, 1949, 1659) showed the presence of xylose (12 parts), arabinose (5 parts), glucose (1 part), and galactose (1 part).

Methylation of Polysaccharide A.—The polysaccharide A (30 g.) was converted into its thallium derivative and methylated twice by Fear and Menzies's method (*loc. cit.*) and four times more with silver oxide and methyl iodide, giving a crisp brown glass (9·3 g.; OMe, 36·6%), purified by dissolution in hot acetone to give methylated polysaccharide A (7·5 g.; OMe, 36·6%; ash, 0·1%).

Hydrolysis of Methylated Polysaccharide A.—The methylated polysaccharide A (7·5 g.) was refluxed with methanolic hydrogen chloride (380 c.c.; 1%) for 12 hr. (constant rotation). At the end of this time the methanolic hydrogen chloride was removed under diminished pressure and the resultant syrup hydrolysed on the water-bath with hydrochloric acid (500 c.c.; 0·5N) for 8 hr. (constant rotation). An insoluble residue (0·42 g.; OMe, 18·0%) was removed at the centrifuge, the clear solution was neutralised with silver carbonate and filtered, and the silver salts were removed with hydrogen sulphide. The solution was finally deionised with Amberlite resins IR-100 and IR-4B, and concentrated to a syrup. Paper-chromatographic examination of the syrup showed the presence of a trimethyl pentose (R_G 0·95), 2 : 3-dimethylxylose, 2 : 3-dimethyl arabinose, a monomethyl pentose (R_G 0·38), and traces of free pentose.

Separation of Methylated Sugars.—The syrupy hydrolysate (5·5 g.) was fractionated on a cellulose column (90 × 3·4 cm.) (Hough, Jones, and Wadman, *J.*, 1949, 2511), elution being carried out with (*a*) light petroleum (b. p. 100—120°)–butanol (7 : 3), saturated with water, (*b*) light petroleum–butanol (1 : 1), saturated with water, and (*c*) butanol, partly saturated with water. The fractions obtained (see Table) were examined by paper chromatography with butanol–ethanol–water–ammonia (40 : 10 : 49 : 1; top layer) as solvent, and in a number of cases the sugars produced after demethylation were examined (Hough, Jones, and Wadman, *J.* 1950, 1702).

Analysis of hydrolysate of methylated polysaccharide A.

Fraction	Wt. of material eluted (g.)	$[\alpha]_D^{16}$	Paper chromatography		Sugar given after demethylation *
			R_G *	Sugar	
1	0·053	—	1·00 (t)	Tetramethyl glucose	—
			0·95	Trimethyl pentose	—
2	0·265	−26·8°	0·95	Trimethyl pentose	Arabinose, xylose (trace), glucose (trace)
3	0·307	−18·3	0·95	Trimethyl pentose	Arabinose, xylose (trace)
4	0·023	+23	0·95	Trimethyl pentose	—
			0·88	Tetramethyl galactose	—
5	0·056	+79·2	·88	Tetramethyl galactose	—
6	0·116	−18·2	0·88 (t)	Tetramethyl galactose	Galactose (trace)
			0·82	Unknown	Arabinose
			0·74 (t)	Dimethyl xylose	Xylose (trace)
7	0·068	+30·8	0·82	Unknown sugar	—
			0·74	Dimethyl xylose	—
8	1·907	+30·0	0·74	Dimethyl xylose	—
9	0·063	+46	0·74	Dimethyl xylose	Xylose, galactose
			0·70	Trimethyl galactose	
10	0·065	+54·7	0·74 (t)	Dimethyl xylose	—
			0·70	Trimethyl galactose	—
			0·64 (t)	Dimethyl arabinose	—
11	0·209	+85·2	0·70	Trimethyl galactose	—
			0·64	Dimethyl arabinose	—
12	0·103	—	0·64 (t)	Dimethyl arabinose	—
			0·38	Monomethyl xylose	—
13	0·559	+34	0·38	Monomethyl xylose	—
14	0·043	—	0·38	Monomethyl xylose	—
			0·36	Dimethyl galactose	—
15	0·119	+71·6	0·36	Dimethyl galactose	Galactose
16	0·067	—	0·36	Dimethyl galactose	—
			0·30 (t)	Unknown	—
17	0·104	—	0·15	Xylose	—
			0·13 (t)	Arabinose	—

* t = trace.

Identification of fractions. 2 : 3 : 5-Trimethyl L-arabinose was identified in fractions 2 and 3 by conversion into 2 : 3 : 5-trimethyl L-arabonamide (m. p. and mixed m. p. 135—136°). An attempt to prepare the aniline derivative of 2 : 3 : 4-trimethyl D-xylose from fraction 3 was unsuccessful. 2 : 3 : 4 : 6-Tetramethyl D-galactose was identified in fraction 5 by conversion into 2 : 3 : 4 : 6-tetramethyl D-galactosylaniline (m. p. and mixed m. p. 194—195°). 2 : 3-Dimethyl D-xylose was identified in fraction 8 by conversion into 2 : 3-dimethyl D-xylosylaniline (m. p. and mixed m. p. 120—122°) and 2 : 3-dimethyl D-xylonamide (m. p. and mixed m. p. 131—132°). 2 : 4 : 6-Trimethyl D-galactose and 2 : 3-dimethyl L-arabinose were identified in fraction 11 by conversion into 2 : 4 : 6-trimethyl D-galactosylaniline (m. p. and mixed m. p. 165—166°) and 2 : 3-dimethyl L-arabonamide (m. p. and mixed m. p. 159—160°) respectively. 2-Methyl D-xylose from fraction 13 crystallised completely from acetone (m. p. and mixed m. p. 134—136°) and was converted into 2-methyl D-xylosylaniline (m. p. and mixed m. p. 124—125°). 2 : 4-Dimethyl D-galactose from fraction 15 was recrystallised from acetone containing 1% of water, giving the monohydrate (m. p. and mixed m. p. 93—96°), and was characterised as 2 : 4-dimethyl D-galactosylaniline (m. p. and mixed m. p. 209—210°) and 2 : 4-dimethyl D-galactonamide (m. p. and mixed m. p. 163—165°).

Quantitative Estimation of Methylated Sugars.—After identification of the fractions obtained from the column the relative proportions of the different sugars were calculated, the results being tabulated below. In the case of fractions containing mixtures of sugars the relative proportions were estimated approximately from the intensities and colours of the spots given on paper chromatograms.

Sugar	Wt. (g.)	Parts per 100 parts of 2 : 3-dimethyl xylose	Sugar	Wt. (g.)	Parts per 100 parts of 2 : 3-dimethyl xylose
Trimethyl pentose	0·636	32	Trimethyl galactose ...	0·160	8
Tetramethyl galactose	0·080	4	Monomethyl xylose ...	0·680	34
Dimethyl xylose	2·000	100	Dimethyl galactose ...	0·160	8
Dimethyl arabinose ...	0·120	6			

On the assumption that trimethyl xylose was present in the same quantity as in the hydrolysate of methylated arabinose-free xylan, 32 parts of trimethyl pentose would contain 3 parts of trimethyl xylose and 29 parts of trimethyl arabinose.

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330. *Hafnium Alkoxides.*

By D. C. BRADLEY, R. C. MEHROTRA, and W. WARDLAW.

The alkoxides of hafnium, $Hf(OR)_4$, where R = Me, Et, Pr^i, Bu^t, and *tert.*-amyl, have been prepared; their boiling points are lower than those of the corresponding zirconium compounds. Hafnium *tert.*-amyloxide has a slightly higher latent heat and entropy of vaporisation and a greater molecular volume than the zirconium analogue. The relative volatilities of zirconium and hafnium alkoxides are discussed.

THE need for hafnium-free zirconium has given a fresh impetus to the study of the chemistry of hafnium. Previous investigation of the comparative chemistry of these elements has been handicapped by the complex nature of their compounds in aqueous solution (cf. Lister and McDonald, *J.*, 1952, 4315). However, by operating in non-aqueous solutions, alkoxides of zirconium and hafnium have been isolated, and their properties suggest a promising means of separation of zirconium and hafnium. In addition, it appeared from the results of fractional distillation (Bradley, Mehrotra, and Wardlaw, *J.*, 1952, 4204) that hafnium *tert.*-amyloxide must be more volatile than its zirconium analogue and this unexpected order of volatilities clearly required further investigation in view of its theoretical importance.

The following alkoxides of hafnium were prepared: $Hf(OR)_4$ where R = Me, Et, Pr^i, Bu^t, and *tert.*-amyl. The tetraethoxide and the tetra*iso*propoxide, $Hf(OPr^i)_4,Pr^iOH$, were obtained by the action of ammonia on pyridinium hafnium hexachloride in benzene in the presence of the appropriate alcohol :

$$(C_5H_5N)_2HfCl_6 + 4ROH + 6NH_3 \longrightarrow Hf(OR)_4 + 6NH_4Cl + 2C_5H_5N$$

The tetramethoxide and the tetra-*tert.*-amyloxide were obtained by interchange of alkoxy-groups with the *iso*propoxide. The action of *tert.*-butyl alcohol on the tetramethoxide gave a solid hafnium methoxide *tert.*-butoxide [probably $Hf(OMe)(OBu^t)_3$] which disproportionated on being heated, forming some hafnium tetra-*tert.*-butoxide. The boiling points of hafnium alkoxides and analogous zirconium compounds are given below :

Alkyl (R)	B. p. of $Hf(OR)_4$	B. p. of $Zr(OR)_4$
Ethyl	180—200°/0·1 mm.	180—200°/0·1 mm.
*iso*Propyl	170°/0·35 mm.	172°/0·35 mm.*
tert.-Butyl	90°/6·5 mm.	92·5°/6·0 mm.
tert.-Amyl	92°/0·1 mm. †	95°/0·1 mm.

* Calc. from 160°/0·1 mm. † Calc. from 106°/0·5 mm.

It is evident that the molecular complexity of hafnium alkoxides must be the same as that of the analogous zirconium derivatives. An important feature of this table is the fact that in no case is a hafnium alkoxide less volatile than its zirconium analogue. The data for the *tert.*-amyloxides confirm the order of volatility Hf > Zr deduced previously (*loc. cit.*, p. 4204).

As a result of b. p. measurements in the pressure range 2·0—10·0 mm. Hg on the *tert.*-amyloxide the latent heat (L_v) and entropy of vaporisation at 5 mm. pressure ($\Delta S_{5\cdot0}$) have been calculated. These results are shown below together with the density ρ (g./c.c) and

Alkoxide	$T_{5\cdot0}$	L_v	a	b	$\Delta S_{5\cdot0}$	ρ	V_l
$Zr(O{\cdot}CMe_2Et)_4$	138·4°	16·2	9·34	3550	39·5	0·975	451·1
$Hf(O{\cdot}CMe_2Et)_4$	136·7°	16·3	9·41	3570	39·8	1·159	454·5

molar volume (V_l c.c.) at 25°. It is not surprising to find the close similarity in latent heat, entropy of vaporisation, or molar volume for these two compounds since the chemical similarity of zirconium and hafnium is well established. However, the order of volatilities Hf > Zr demands examination. It follows from the Clausius–Clapeyron equation that the relative volatility P_{Zr}/P_{Hf} over a small temperature range will take the form :

$$\log_{10} P_{Zr}/P_{Hf} = (a_{Zr} - a_{Hf}) - (b_{Zr} - b_{Hf})/T$$

In the case where $b_{Zr} \simeq b_{Hf}$ the temperature-independent terms a_{Zr} and a_{Hf} will assume major importance. It is noteworthy that for the relative volatilities P_1/P_2 of solid monatomic compounds the difference between the temperature-independent terms a_1 and a_2 can be calculated by the method of statistical thermodynamics and reduces to the simple form $a_1 - a_2 = \frac{3}{2} \log_{10} M_1/M_2$, where M_1 and M_2 are the molecular weights. Hence for $b_1 = b_2$ it follows that $\log_{10} P_1/P_2 = \frac{3}{2} \log_{10} M_1/M_2$ and the substance with the greater molecular weight is the more volatile. For polyatomic molecules $a_1 - a_2$ will exceed $\frac{3}{2} \log_{10} M_1/M_2$ by an amount which is determined by a function of the ratios of the various moments of inertia, *e.g.*, $\frac{1}{2} \log_{10} (I_A \times I_B \cdots I_H/I_P \times I_Q \cdots I_Z)$, and whose complexity depends on the number and arrangements of atoms in the molecule. Since molecular weight is included in the moment of inertia, it is evident that in polyatomic molecules (with $b_1 = b_2$) there is a possibility that this " molecular-weight effect " will enhance the greater volatility of the compound with higher molecular weight.

With regard to the *tert.*-amyloxides of zirconium and hafnium, our data show $b_{Hf} > b_{Zr}$ and $a_{Hf} > a_{Zr}$, which suggests that in spite of greater intermolecular attraction in the hafnium compound its higher molecular weight leads to a greater volatility. However, it is realised that a variation of 1% would reverse the orders to $a_{Zr} > a_{Hf}$ and $b_{Zr} > b_{Hf}$ and more accurate vapour-pressure determinations (now in progress) are required before a confident explanation for the observed volatility order can be advanced. It is noteworthy that in the borohydrides $M(BH_4)_4$ (Hoekstra and Katz, *J. Amer. Chem. Soc.*, **1949**, **71**, 2488), which are the most volatile known compounds of zirconium or hafnium, the hafnium compound is the more volatile and again $a_{Hf} > a_{Zr}$ and $b_{Hf} > b_{Zr}$. Moreover, the relative volatility P_{Hf}/P_{Zr} is greater in the borohydrides where $M_{Hf}/M_{Zr} = 1{\cdot}58$ than in the *tert.*-amyloxides where $M_{Hf}/M_{Zr} = 1{\cdot}18$, in qualitative agreement with the above theory.

Experimental

All-glass apparatus was used and special precautions were taken to exclude moisture. The methods of analysing the alkoxides and of purifying and drying solvent and alcohols were the same as previously described (*loc. cit.*). Boiling-point determinations were carried out in the same apparatus under the same conditions as for the zirconium compounds. A micro-dilatometer (0·65 c.c.) containing two vertical calibrated " Veridia " capillaries (bore 1 mm.) was used for density determinations. The alkoxides were collected in the dilatometer by distillation at 0·1 mm.

Preparation of Pyridinium Hafnium Hexachloride from Hafnia.—Hafnium oxide (10·0 g.) was fused with potassium hydrogen sulphate (145 g.), and the cooled clear melt dissolved in water. Hafnium hydroxide (precipitated by ammonia solution, *d* 0·88) was dissolved in the minimum amount of hydrochloric acid (*d* 1·18), and hydrated hafnium oxychloride obtained by evaporation. The oxychloride (15·2 g.) in ethyl alcohol (200 c.c.) was treated with excess of hydrogen chloride followed by pyridine (8·0 g.). The crystalline *pyridinium hafnium hexachloride* (20·8 g.) was filtered off and dried at 120°/0·5 mm. [Found : Hf, 32·5; Cl, 38·4. $(C_5H_6N)_2HfCl_6$ requires Hf, 32·4; Cl, 38·6%].

Preparation of Hafnium iso*Propoxide.*—The complex hafnium chloride (20·2 g.), suspended in benzene (134 g.) and *iso*propyl alcohol (26·5 g.), was treated with excess of ammonia. After removal of ammonium chloride, the solution was evaporated to dryness, and the product heated

at 120°/0·5 mm. The solid (9·4 g.) was crystallised from boiling *iso*propyl alcohol (130 c.c.), and the crystalline hafnium *iso*propoxide *solvate* (9·0 g.) obtained was dried at 40°/0·5 mm. [Found: Hf, 37·8. $Hf(OPr^i)_4,Pr^iOH$ requires Hf, 37·6%]. The foregoing product lost *iso*propanol at 120—130°/0·5 mm. and *hafnium tetra*iso*propoxide* was obtained by distillation (b. p. 170°/0·35 mm., 188°/2·5 mm.) as a colourless solid (6·0 g.) [Found: Hf, 43·1. $Hf(OPr^i)_4$ requires Hf, 43·1%].

Hafnium Tetraethoxide.—The complex hafnium chloride (11·6 g.), suspended in benzene (80 c.c.), was treated with ethyl alcohol (39·5 g.) and excess of ammonia. After removal of ammonium chloride, the solution was evaporated under reduced pressure and gave a white solid, which was heated at 160°/0·2 mm. to remove traces of pyridine. The *ethoxide* melted at *ca.* 180°/0·2 mm. and was distilled in the range 180—200°, giving a white solid distillate (7·1 g.) [Found: Hf, 50·1. $Hf(OEt)_4$ requires Hf, 49·8%].

Hafnium Tetramethoxide.—Addition of methyl alcohol (50 c.c.) to a solution of hafnium *iso*propoxide (6·7 g.) in benzene (100 c.c.) caused immediate precipitation of a white solid. The mixture was heated at 70—80° for 8 hr., and the solvent removed by evaporation. The *hafnium methoxide* was dried at 160°/0·1 mm. for 2 hr. and, like zirconium methoxide, was found to be insoluble in the common organic solvents [Found: Hf, 59·0. $Hf(OMe)_4$ requires Hf, 59·0%].

Hafnium Tetra-tert.-*butoxide.*—Hafnium methoxide (6·7 g.) was heated at 140° with *tert.*-butyl alcohol (27 g.) in benzene under an efficient fractionating column fitted with a total-condensation variable take-off still-head. The methoxide required 6 hr. to dissolve completely and fractionation was continued for a further 8 hr. After removal of solvent the remaining solid was heated at 8—9 mm. and melted at 120°. The liquid started refluxing at 200—220° and a colourless mobile liquid was distilled at 250°. This distillate was redistilled (b. p. 90°/6·5 mm.) and proved to be *hafnium* tert.-*butoxide* [Found: Hf, 38·1. $Hf(OBu^t)_4$ requires Hf, 37·9%].

Hafnium Tetra-tert.-*amyloxide.*—Hafnium tetra*iso*propoxide (9·3 g.) was treated with *tert.*-amyl alcohol (12·7 g.) in benzene (67 g.) at 140° until no more benzene–*iso*propyl alcohol azeotrope was collected by fractionation. The *hafnium* tert.-*amyloxide* which remained after the removal of solvent was distilled (b. p. 91°/0·1 mm.) and gave a colourless mobile distillate (8·6 g.) [Found: Hf, 33·9. $Hf(OC_5H_{11})_4$ requires Hf, 33·9%]; b. p.s were 106°/0·5; 123°/2·2; 125·5°/2·5; 130°/3·5; 134°/4·5; 139°/5·6; 140°/6·0; 142°/6·8; 146°/8·0; 148°/8·8; 149·5°/9·5; 150°/10·0 mm. Densities determined at 25·00° on this compound and on zirconium *tert.*-amyloxide were: $Hf(OC_5H_{11})_4$, $\rho = 1{\cdot}159 \pm 0{\cdot}003$ g./c.c. $Zr(OC_5H_{11})_4$, $\rho = 0{\cdot}975 \pm 0{\cdot}002$ g./c.c.

Spectrographic analysis showed that the sample of hafnium oxide used for this work contained: HfO_2, 98·5; ZrO_2, *ca.* 1·5%. We thank Mr. F. Hudswell, of A.E.R.E., Harwell, for conducting this analysis.

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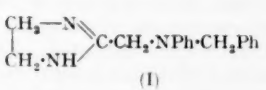
331. 2-*Thymyloxymethylglyoxalines and Related Compounds as Potential Antihistamines.*

By H. BADER and J. D. DOWNER.

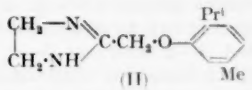
8-Thymyloxymethylcaffeine and a number of substituted 2-thymyloxymethylglyoxalines and thymyloxyacetamidines have been prepared. Some of the compounds possessed antihistamine activity.

ALTHOUGH histamine contains a glyoxaline ring the number of glyoxalines prepared specifically as potential antihistamines is small (Carrara, D'Amato, and Pagani, *Chimica e industria* (*Milan*), **1946**, **28**, 9; Ellinger and Goldberg, *J.*, 1949, 263; Huebner, Turner, and Scholz, *J. Amer. Chem. Soc.*, 1949, **71**, 2801; 3942; Tilford, Van Campen, Jr., and Shelton, *ibid.*, p. 1885; Wright, *ibid.*, p. 2035; Ruoff and Scott, *ibid.*, 1950, **72**, 4950). Several compounds containing a dihydroglyoxaline ring have been prepared which possess con-

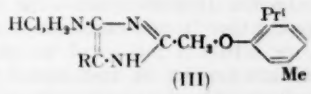
siderable antihistamine activity, including antazoline (I) and 4 : 5-dihydro-2-thymyloxymethylglyoxaline (II) (Djerassi and Scholz, *ibid.*, 1947, **69**, 1688). It was of interest therefore to examine glyoxaline analogues of (II) as potential antihistamines.



(I)

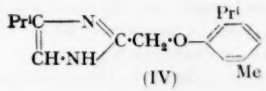


(II)

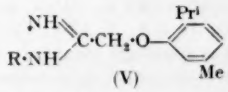


(III)

4-Amino-2-thymyloxymethylglyoxalines (III; R = Pr^i, Ph or CO_2Et) were prepared (cf. Cook, Davis, Heilbron, and Thomas, *J.*, 1949, 1071) by condensation of benzyl thymyloxyacetothioimidate hydrochloride with the appropriate α-amino-nitrile in boiling chloroform. Similarly, 4-amino-2-phenoxymethyl-5-phenylglyoxaline hydrochloride was obtained from α-aminobenzyl cyanide and benzyl phenoxyacetothioimidate hydrochloride. Good yields were obtained except in the case of (III; R = Pr^i) where much ammonium chloride was formed. With α-aminopropionitrile and benzyl thymyloxyacetothioimidate hydrochloride, ammonium chloride was formed almost quantitatively. On the other hand, α-aminoacetonitrile with the same thioimidate hydrochloride at room temperature in the presence of pyridine yielded the glyoxaline (III; R = H) (cf. Bader, Downer, and Driver, *J.*, 1950, 2775).



(IV)



(V)

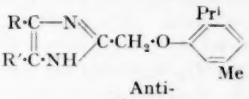
The glyoxaline (IV) was prepared by condensing benzyl thymyloxyacetothioimidate hydrochloride with 1-amino-3-methylbutan-2-one hydrochloride according to Ellinger and Goldberg's method (*loc. cit.*). A small amount of an unidentified compound, m. p. >250°, was also formed. The amino-ketone was obtained from 1-chloro-3-methylbutan-2-one by a Gabriel synthesis.

Many xanthines, including caffeine, have been found useful in the treatment of allergic conditions (Emmelin, Kahlson, and Lindstrom, *Acta physiol. scand.*, 1941, **3**, 39) and have the advantage of being non-toxic. The glyoxaline (III; R = CO_2Et) was therefore converted into 8-thymyloxycaffeine by ring-closure of its 4-methylureido-derivative, according to the method of Cook, Heilbron, Macdonald, and Mahadevan (*J.*, 1949, 1064), and methylation of the product with methyl iodide.

Djerassi and Scholz (*loc. cit.*) found that *N*-alkyl-thymyloxyacetamidines possessed greater activity than 4 : 5-dihydro-2-thymyloxymethylglyoxaline. Similar compounds (V; R = H, Me, Pr^i, and Bu^i) were therefore prepared from the imidate hydrochlorides and excess of ammonia or the appropriate amine. The amidine (V; R = H) has been previously described (G.P. 684,945; Djerassi and Scholz, *loc. cit.*).

Pharmacological results are summarised in the annexed Table.

Glyoxalines,



Amidines,

R	R′	Anti-histamine activity (γ/ml.[a])	Toxicity (mg./kg.[b])
NH_2	H	[d]	Non-toxic, 160
H	Pr^i	40	Non-toxic, 160
NH_2	Pr^i	100	Non-toxic, 160
NH·CO·NHMe	Pr^i	40	—
NH_2	Ph	d.	—
NH_2	CO_2Et	d.	—

R	Anti-histamine activity (γ/ml.[a])	Toxicity (mg./kg.[b])
CH_2·C(:NH)·NH_2 [c]	10—15	Non-toxic, 160
CH_2·C(:NH)·NHMe	100	—
CH_2·C(:NH)·NHPr^i	10	Non-toxic, 160
CH_2·C(:NH)·NHBu^i	40	80
8-Thymyloxycaffeine	100	—

[a] γ of compound per ml. of solution added to the bath-liquid, equivalent to the reduction in contraction of an isolated guinea-pig gut caused by 1 γ of antazoline sulphate. [b] LD_{50}, mice. [c] Djerassi and Scholz (*loc. cit.*) give 1—10. [d] >100.

Experimental

Nitriles.—Phenoxy- and thymyloxy-acetonitriles were prepared by Djerassi and Scholz's method (*loc. cit.*).

Imidate Hydrochlorides.—The following general method, essentially that of Pinner ("Die Imido Ether"), was employed. Excess of dry hydrogen chloride was passed into a mixture of the nitrile (1 mol.) and the alcohol (1—2 mols.) at 0—5° in the diluent indicated. The resultant product was then kept (1 hr. to 3 days) at 0° until the imidate hydrochloride separated. The hydrochlorides prepared (not purified) are tabulated and where possible analyses (by titration against standard alkali).

Imidate hydrochlorides, $CRR'{:}NH,HCl$.

R	R′	Solvent	Yield (%)	M. p.	Formula	HCl (%) Found	HCl (%) Reqd.
$CH_3{\cdot}OPh$	$S{\cdot}CH_2Ph$	Et_2O	83	134°	—	—	—
5 : 2 : 1-$C_6H_3MePr^i{\cdot}O{\cdot}CH_2$–	OEt	$CHCl_3$	60	110—112 [a]	$C_{14}H_{22}O_2NCl$	13·0	13·4
,,	$S{\cdot}CH_2Ph$	Et_2O	68	173	$C_{19}H_{24}ONSCl$	10·7	10·4

[a] Djerassi and Scholz (*loc. cit.*) give m. p. 109·5—110°.

4-*Amino*-2-*phenoxymethyl*-5-*phenylglyoxaline* *Hydrochloride*.—Benzyl phenoxyacetothioimidate hydrochloride (29·4 g.), α-aminobenzyl cyanide (13·6 g.), and chloroform (100 c.c.) were refluxed for 2 hr., and the precipitated solid was filtered off and washed with chloroform, to give the *glyoxaline* (23 g., 74%), m. p. 167° (unchanged by crystallisation from ethanol) (Found: C, 64·0; H, 5·8; N, 13·6; Cl, 11·6. $C_{16}H_{16}ON_3Cl$ requires C, 63·7; H, 5·35; N, 13·9; Cl, 11·75%). It is sparingly soluble in water and can be diazotised.

4-*Amino*-2-*thymyloxymethylglyoxaline* *Hydrochloride*.—Benzyl thymyloxyacetothioimidate hydrochloride (10 g.), chloroform (60 c.c.), pyridine (2·5 c.c.), and aminoacetonitrile (1·6 g.) were mixed in the above order and shaken under nitrogen for 15 min. Ethanolic hydrogen chloride (20 c.c. of 8·7%) was added to the cold solution with stirring, and the mixture diluted with ethyl acetate (2 vol.) and left at 0°. The precipitate (6·3 g., 75%), m. p. 170° (decomp.), recrystallised from methanol (charcoal) as needles of **4-*amino*-2-*thymyloxymethylglyoxaline* *hydrochloride***, m. p. 170° (decomp.) (Found: C, 59·95; H, 7·05; N, 14·7; Cl, 12·5. $C_{14}H_{20}ON_3Cl$ requires C, 59·65; H, 7·15; N, 14·9; Cl, 12·6%). It is readily soluble in warm water and can be diazotised.

4-*Amino*-5-iso*propyl*-2-*thymyloxymethylglyoxaline* *Hydrochloride*.—Benzyl thymyloxyacetothioimidate hydrochloride (7·5 g.), α-amino*iso*valeronitrile (2·1 g.), and chloroform (20 c.c.) were refluxed for 3 hr., the mixture was filtered, and the filtrate diluted with ether (200 c.c.) and kept at 0° for 30 min. The crystals that had separated were triturated with ethanol (25 c.c.) at 0° and the undissolved ammonium chloride was filtered off. The filtrate was diluted with ether (80 c.c.) and kept overnight. Recrystallisation of the solid (1·5 g.), so obtained, from ethanol–ethyl acetate gave colourless needles of **4-*amino*-5-iso*propyl*-2-*thymyloxymethylglyoxaline* *hydrochloride***, m. p. 157° (Found: C, 62·7; H, 8·2; N, 12·8; Cl, 10·95. $C_{17}H_{26}ON_3Cl$ requires C, 63·0; H, 8·1; N, 13·0; Cl, 10·95%). Light absorption (ethanol): $\lambda_{max.}$ 2710 Å, ε 6300. It gave a red dye on diazotisation and coupling with β-naphthol.

4-N′-*Methylureido*-5-iso*propyl*-2-*thymyloxymethylglyoxaline*.—Methyl *iso*cyanate (4·5 c.c.) was added in three portions at 0° to the preceding glyoxaline hydrochloride (3 g.) in pyridine (15 c.c.), and the mixture warmed at 100° for 20 min. after each addition. The resultant mixture on dilution with ethanol (20 c.c.) and water (30 c.c.) yielded 4-N′-*methylureido*-5-iso*propyl*-2-*thymyloxymethylglyoxaline* (2·2 g.), which recrystallised from 50% aqueous ethanol as colourless needles, m. p. 156° (Found: C, 66·05; H, 7·95; N, 16·7. $C_{19}H_{28}O_2N_4$ requires C, 66·2; H, 8·2; N, 16·3%).

4-*Amino*-5-*phenyl*-2-*thymyloxymethylglyoxaline* *Hydrochloride*.—Benzyl thymyloxyacetothioimidate hydrochloride (20 g.), α-aminobenzyl cyanide (7·7 g.), and chloroform (90 c.c.) were refluxed for 3·5 hr., and the solid formed (17 g., 80%), m. p. 176°, was collected and crystallised from methanol (250 c.c.), to give colourless needles of **4-*amino*-5-*phenyl*-2-*thymyloxymethylglyoxaline* *hydrochloride***, m. p. 183° (decomp.) (Found: C, 67·0; H, 6·75; N, 11·4; Cl, 10·05. $C_{20}H_{24}ON_3Cl$ requires C, 67·1; H, 6·75; N, 11·7; Cl, 9·9%). It gave a red dye on diazotisation and coupling with β-naphthol.

***Ethyl* 4-*Amino*-2-*thymyloxymethylglyoxaline*-5-*carboxylate* *Hydrochloride*.**—Benzyl thymyloxyacetothioimidate hydrochloride (30 g.), chloroform (50 c.c.), and ethyl α-aminocyanoacetate

(15 g.) were refluxed for 4 hr. A small quantity of ammonium chloride was removed and the filtrate evaporated to dryness *in vacuo*. The residue was triturated with ethanol (2·2 c.c.), diluted with ether, and filtered. The solid (24·8 g., 81·8%), m. p. 150°, crystallised from ethanol, to give *ethyl 4-amino-2-thymyloxymethylglyoxaline-5-carboxylate hydrochloride*, m. p. 154° (Found: C, 57·7; H, 6·95; N, 11·9. $C_{17}H_{24}O_3N_3Cl$ requires C, 57·7; H, 6·85; N, 11·9%). The base, m. p. 146°, could be obtained by trituration of the hydrochloride with aqueous sodium carbonate solution.

8-Thymyloxymethylcaffeine.—Methyl *iso*cyanate (13·5 g.) was added in three portions at 0° to the preceding glyoxaline hydrochloride (16·9 g.) in pyridine (30 c.c.), and the mixture gently refluxed for 20 min. after each addition. The pyridine was removed *in vacuo*, the crude methylureido-derivative dissolved in aqueous sodium hydroxide (300 c.c. of 10%) at 60°, water (300 c.c.) added, and a small amount of insoluble material (not examined) removed. Ethanol (600 c.c.) was added to the filtrate which was then neutralised with 30% aqueous acetic acid and kept at 0° overnight. The xanthine (4·2 g., 27%), m. p. 256°, which had separated was purified by dissolution in aqueous ethanolic sodium hydroxide and precipitation with acetic acid, to give *1-methyl-8-thymyloxymethylxanthine*, m. p. 256° (Found: N, 17·15. $C_{17}H_{20}O_3N_4$ requires N, 17·05%). The xanthine (2 g.) and methyl iodide (5 g.) in aqueous sodium hydroxide (30 c.c. of 5%) were heated at 100—110° for 2 hr. The gum (1·82 g.) formed was removed and dissolved in chloroform (charcoal), the solution concentrated to 10 c.c., and ether added until the solution became faintly turbid. After 1 hr. at 0° the precipitate (0·21 g.), m. p. 250° (mainly unchanged xanthine), was removed. The filtrate was kept for 2 hr. at 0° and the solid (0·52 g., 24%), m. p. 154°, that had separated was crystallised from chloroform–ether, to give colourless plates of *8-thymyloxymethylcaffeine*, m. p. 154° (Found: C, 63·2; H, 6·55; N, 15·9. $C_{19}H_{24}O_3N_4$ requires C, 64·0; H, 6·9; N, 15·7%). It gave a positive murexide colour.

1-Amino-3-methylbutan-2-one Hydrochloride.—1-Chloro-3-methylbutan-2-one (29 g.), potassium phthalimide (25 g.), and dry xylene (25 c.c.) were heated under reflux at 120—130° for 1 hr., the xylene and unchanged chloride were removed by steam-distillation, and the residue was cooled and filtered. The crude solid (35 g., 64%), m. p. 82—90°, was crystallised from ethanol (200 c.c.), to give colourless needles of *3-methyl-1-phthalimidobutan-2-one* (31 g.), m. p. 102° (Found: C, 67·35; H, 5·95; N, 6·05. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·65; N, 6·05%). This (25 g.) was suspended in aqueous hydrochloric acid (275 c.c. of 30%) and refluxed for 8 hr. The phthalic acid was then removed and the solution evaporated *in vacuo* at 50°. The residue was recrystallised from 50% ethanol–ether (120 c.c.) to give colourless plates of *1-amino-3-methylbutan-2-one hydrochloride* (13 g., 90%), m. p. 164° (Found: C, 43·25; H, 8·85; N, 10·2; Cl, 25·85. $C_5H_{12}ONCl$ requires C, 43·6; H, 8·8; N, 10·2; Cl, 25·8%).

4-iso*Propyl-2-thymyloxymethylglyoxaline*.—Benzyl thymyloxyacetothioimidate hydrochloride (10 g.) was added portion-wise during 10 min. to a solution of sodium (0·84 g.) in dry ethanol (35 c.c.) with stirring at −10° to −5° in an atmosphere of nitrogen. After 15 min. a solution of the above amino-ketone hydrochloride (3·93 g.) in ethanol (70 c.c.) was added, during 30 min., at −5°. The mixture was stirred at −5° for 1 hr., then kept at room temperature for 24 hr. Sodium (0·42 g.), dissolved in ethanol (25 c.c.), was then added at −5° and the mixture left for 4 days at room temperature. Sodium chloride (2·7 g., 85%) was removed and the solution evaporated *in vacuo* at 50° to leave a yellow oil. To this, ethanolic hydrogen chloride (40 c.c. of 5%) was added followed by ether (100 c.c.) and unchanged thioimidate hydrochloride (1·6 g.) thus precipitated was removed. The remainder was diluted with ether (350 c.c.) and kept at 0° overnight. The solid (0·3 g.) which had separated was crystallised from methanol–ether, to give colourless crystals of a *substance*, decomp. >250° (Found: C, 48·2; H, 8·9; N, 14·3; Cl, 27·4. $C_{16}H_{35}N_4Cl_3$ requires C, 49·25; H, 9·05; N, 14·4; Cl, 27·3%). It gave no Pauly reaction and was not further examined. The main filtrate was evaporated *in vacuo* at 40°, and the yellow oily residue diluted with water (150 c.c.) and steam-distilled to remove toluene-ω-thiol (2 g.). The non-volatile residue was extracted with ether and the ethereal extract evaporated *in vacuo* to give a gum (4·5 g.). This was rubbed with warm water, made alkaline with dilute aqueous sodium carbonate, and extracted into chloroform. Removal of the chloroform gave a gum (4 g.) which crystallised (charcoal) from ethanol (75 c.c.)–water (70 c.c.) (or benzene–light petroleum), to give colourless prisms of 4-iso*propyl-2-thymyloxymethylglyoxaline* (2·5 g.), m. p. 97° (Found: C, 74·6; H, 9·1; N, 10·0. $C_{17}H_{24}ON_2$ requires C, 74·95; H, 8·9; N, 10·3%). Light absorption (ethanol): $\lambda_{max.}$ 2735 Å, ε 1900. It gave a positive Pauly reaction.

Thymyloxyacetamidine Hydrochloride.—Benzyl thymyloxyacetothioimidate hydrochloride (10 g.) and ethanolic ammonia (55 c.c. of 10%) were shaken until homogeneous and the solution

kept at room temperature for 6 days. Ammonia was removed *in vacuo*, and the residue treated with ethanolic hydrogen chloride (20 c.c. of 8%) and cautiously diluted with ether to 250 c.c., whereupon a small amount of ammonium chloride was precipitated. This was filtered off and the solution kept overnight at 0°; thymyloxyacetamidine hydrochloride (3·0 g.) separated. A further crop (3·1 g.) was obtained by concentration of the mother-liquor. It recrystallised from methanol–ether as needles, m. p. 185° (Djerassi and Scholz, *loc. cit.*, give m. p. 185—185·5°) (Found: C, 59·5; H, 7·7; N, 11·6; Cl, 14·6. Calc. for $C_{12}H_{19}ON_2Cl$: C, 59·35; H, 8·0; N, 11·55; Cl, 14·6%).

The same amidine was obtained by the method of Partridge and Short (*J.*, 1947, 390), by heating thymyloxyacetonitrile (18 g.) and ammonium thiocyanate (29 g.) at 180° for 90 min. with vigorous stirring. After cooling, the product was boiled with water (40 c.c.) and poured on ice (40 g.) and aqueous sodium hydroxide (30 c.c. of 10%). The oily suspension was extracted into ether (400 c.c.), the extract washed, and the product re-extracted with 10% hydrochloric acid (3 × 50 c.c.). On concentration of the extract to 250 c.c. *in vacuo*, the amidine hydrochloride (7 g.) separated.

N-*Methyl-α-thymyloxyacetamidine Hydrochloride.*—A mixture of benzyl thymyloxyacetothioimidate hydrochloride (15 g.) and methylamine (20 g.) in methanol (100 c.c.) was kept at room temperature for 6 days. The excess of methylamine was then removed at room temperature, ethanolic hydrogen chloride (35 c.c. of 10%) added, followed by ether (300 c.c.), and the solution kept at 0° for 1 hr. Methylamine hydrochloride which had deposited was removed, ether (200 c.c.) added to the filtrate, and the latter kept at 0° for 3 hr. N-*Methyl-α-thymyloxyacetamidine hydrochloride* (5·4 g.) separated as prisms, m. p. 173° (unchanged by crystallisation from ethanol–ether) (Found: N, 10·2; Cl, 13·7. $C_{13}H_{21}ON_2Cl$ requires N, 10·9; Cl, 13·8%). Concentration of the mother-liquor to small volume and dilution with ether gave a further crop (4·6 g.), m. p. 166° (total yield, 91%).

N-iso*Propyl-α-thymyloxyacetamidine Hydrochloride.*—A solution of *iso*propylamine (8 c.c.) and benzyl thymyloxyacetothioimidate hydrochloride (10 g.) in dry methanol (40 c.c.) was kept at room temperature for 5 days, the excess of amine removed, and the solution concentrated *in vacuo* at 25° to *ca.* 20 c.c. Ethanolic hydrogen chloride was then added and the solution diluted with ether (120 c.c.) until just turbid. The solid (2·5 g.), m. p. 114°, which separated after several days was crystallised from ethanol–ether, to give colourless needles of N-iso*propyl-α-thymyloxyacetamidine hydrochloride*, m. p. 115° (Found: N, 10·1; Cl, 12·75. $C_{15}H_{25}ON_2Cl$ requires N, 9·8; Cl, 12·45%).

N-iso*Butyl-α-thymyloxyacetamidine Hydrochloride.*—*iso*Butylamine (10 g.), benzyl thymyloxyacetothioimidate hydrochloride (15 g.), and dry ethanol (150 c.c.) were mixed at 0° and the clear solution kept under nitrogen for 1 week. Most of the excess of amine was removed by concentration *in vacuo* to small volume, ethanolic hydrogen chloride (75 c.c. of 7%) added, and the mixture again concentrated to small volume at 30°. Ethyl acetate (100 c.c.) was added, followed by ether (*ca.* 300 c.c.) until the solution was just cloudy; it was then kept at 0° overnight. *iso*-Butylamine hydrochloride that had separated was removed, the filtrate evaporated to an oil *in vacuo* at 30°, water (200 c.c.) added, and the suspended toluene-ω-thiol extracted with ether. Dissolved ether was removed from the aqueous layer, potassium carbonate (20 g.) added, and the crude *amidine* (12·8 g.) isolated by extraction with chloroform. This was triturated with ethanolic hydrogen chloride (25 c.c. of 3%) and the hygroscopic colourless needles of N-iso*butyl-α-thymyloxyacetamidine hydrochloride* (5 g.) m. p. 93° (unchanged by crystallisation from ethanol–ether), were collected (Found: N, 9·7; Cl, 11·9. $C_{16}H_{27}ON_2Cl$ requires N, 9·35; Cl, 11·95%).

The authors thank Sir Ian Heilbron, F.R.S., and Dr. A. H. Cook, F.R.S., for valuable discussions, and the Directors of these Laboratories for permission to publish this paper.

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332. 1 : 3 : 7 : 8-*Tetramethylxanthine.*

By H. Bader and J. D. Downer.

In order to compare their pharmacological properties caffeine and its 8-methyl derivative (1 : 3 : 7 : 8-tetramethylxanthine) have been synthesized by the method of Cook *et al.* (*J.*, 1949, 1071; 1950, 1884). The preparation of 1-methyl-2-thioxanthine required for caffeine has been simplified with improved yield (62%) by omitting the isolation of the intermediate 4-amino-5-carbethoxyglyoxaline and its *N'*-methylthioureido-derivative, and using pyridine as a solvent.

Experimental.—Diazomethane (21 g.) in ether (750 c.c.) was added to ethyl 4-amino-2-methylglyoxaline-5-carboxylate (18·8 g.) in methanol (100 c.c.) and kept at room temperature for 4 days. The solvents were removed *in vacuo*; the residue crystallized from benzene as colourless needles of *ethyl 4-amino-1 : 2-dimethylglyoxaline-5-carboxylate* (17·1 g., 84%), m. p. 121° (Found: C, 51·7; H, 6·9. $C_8H_{13}O_2N_3$ requires C, 52·4; H, 7·15%). (For light absorption properties, see Bader, Downer, and Driver, *J.*, 1950, 2775.)

This dimethylglyoxaline (16·9 g.), methyl *iso*thiocyanate (10 g.), and pyridine (20 c.c.) were refluxed for 2 hr., cooled, and filtered. The resulting *ethyl 1 : 2-dimethyl-4-N'-methylthioureido-glyoxaline-5-carboxylate* (15·6 g., 66%), m. p. 164°, crystallized from ethanol as colourless needles, m. p. 166·5° (Found: C, 47·0; H, 6·45; N, 22·3. $C_{10}H_{16}O_2N_4S$ requires C, 46·85; H, 6·3; N, 21·9%).

This (15·1 g.) was dissolved in aqueous ammonia (450 c.c. of 30%) at 60° and the crude xanthine [11·55 g., 93%; m. p. 345° (decomp.)] precipitated by addition of 30% aqueous acetic acid. Repeated precipitation with acetic acid of its solution in aqueous ammonia gave colourless needles of *1 : 7 : 8-trimethyl-2-thioxanthine*, 365° (decomp.) (Found: C, 45·65; H, 4·75; N, 26·2. $C_8H_{10}ON_4S$ requires C, 45·7; H, 4·8; N, 26·6%).

Hydrogen peroxide (50 c.c.; 80-vol.) was added in portions to a suspension of 1 : 7 : 8-trimethyl-2-thioxanthine (11·1 g.) in concentrated aqueous ammonia (100 c.c.) with vigorous stirring, and the mixture brought to the boil. When the reaction had subsided hydrogen peroxide (50 c.c.; 80-vol.) was added, stirring continued for 10 min. and the crude xanthine (7·35 g., 70%; m. p. 338°) precipitated with acetic acid. Recrystallization from methanol gave colourless needles of *1 : 7 : 8-trimethylxanthine*, m. p. 344° (decomp.) (Found: C, 49·1; H, 5·0; N, 28·6. $C_8H_{10}O_2N_4$ requires C, 49·5; H, 5·2; N, 28·85%).

Diazomethane (7·5 g.) in ether (250 c.c.) was added to a suspension of the preceding xanthine (7·2 g.) in methanol (100 c.c.) at 0° and the whole kept at room temperature for 18 hr. The solvent was concentrated *in vacuo* to 20 c.c., whereupon needles of 1 : 3 : 7 : 8-tetramethylxanthine (8-methylcaffeine) (6·2 g., 80%), m. p. 209° undepressed by authentic material, were deposited.

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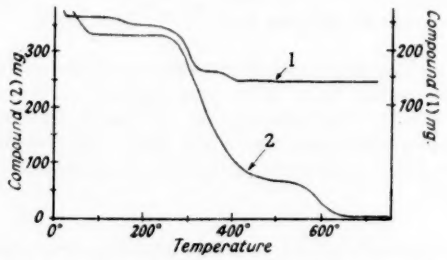
333. *Thermogravimetric Curves for the Decomposition of Octa-ammino-μ-amino-μ-nitrodicobaltic Sulphate and Dichlorobisethylenediaminocobaltic Hexachlorostibnate.*

By D. Gibbons.

The precipitates obtained by use of Belcher and Gibbon's new reagents (see title) for the determination of sulphate (*J.*, 1952, 4216) and antimony (*J.*, 1952, 4775) have been examined by Professor C. Duval by means of his thermogravimetric balance. The curves obtained are shown in the Figure: (1) is for the decomposition of octa-ammino-μ-amino-

μ-nitrodicobaltic sulphate, and (2) for that of dichlorobisethylenediaminocobaltic hexachlorostibnate. Both show well-defined horizontal portions extending on each side of the



drying ranges previously recommended, so that the safety limits may be extended to 25—122° and 75—225°, respectively.

I thank Professor Duval for permission to reproduce these curves.

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334. C-*Methylation of* 4 : 6-*Dihydroxycoumaran*-3-*one.*

By T. P. C. MULHOLLAND and G. WARD.

FOR synthesis of compounds related to dechlorogriseofulvin (MacMillan, *J.*, in the press), 4 : 6-dimethoxycoumaranone was required in quantity. Although this was achieved by a slight modification of the method of Drumm, MacMahon, and Ryan (*Proc. Roy. Irish Acad.*, 1924, **36**, 149), methylation of 4 : 6-dihydroxycoumaranone with methyl sulphate under their conditions gave an impure product which could not be fractionated by crystallisation. Chromatography showed it to consist of 4 : 6-dimethoxycoumaranone and a ketone $C_{11}H_{12}O_4$ containing one *C*-methyl group.

On the assumption that the latter compound was a *C*-methyl derivative of 4 : 6-dimethoxycoumaranone, the ready reaction with benzaldehyde to give a benzylidene derivative, and the condensation in the presence of alkali to give a compound $C_{22}H_{22}O_7$ showed that *C*-methylation had taken place in the phloroglucinol nucleus giving 4 : 6-dimethoxy-5(or 7)-methylcoumaranone. The 5-methyl structure was established by unambiguous synthesis from 4-hydroxy-2 : 6-dimethoxytoluene *via* ω-chloro-2-hydroxy-4 : 6-dimethoxy-5-methylacetophenone. The 7-methyl isomer was also synthesised. Neither coumaranone gave the violet colour with concentrated nitric acid given by dechlorogriseofulvin (MacMillan, *loc. cit.*) and 4 : 6-dimethoxycoumaranone.

Experimental.—Some microanalyses are by Mr. W. Brown.

Methylation of 4 : 6-*dihydroxycoumaranone.* (i) A suspension of 4 : 6-dihydroxycoumaranone (50 g.) in water (125 ml.) was treated with potassium hydroxide (35 g.) in water (70 ml.). Methyl sulphate (118 ml.) was added dropwise to the stirred mixture at 25° during 2 hours, the pH being maintained at 7—8 by addition of more alkali. More methyl sulphate (20 ml.) and alkali were then added, the pH being raised to 8—10 towards the end of the reaction. The insoluble product was washed with cold methanol and crystallised twice from benzene, giving 4 : 6-dimethoxycoumaranone (24 g.), m. p. 134—137°. Further crystallisation raised the m. p. to 138—139° (Found : C, 61·75; H, 5·4. Calc. for $C_{10}H_{10}O_4$: C, 61·8; H, 5·2%).

(ii) Methylation of 4 : 6-dihydroxycoumaranone (50 g.) by the method of Drumm *et al.* (*loc. cit.*) gave 54 g. of crude neutral product. This (10 g.) was chromatographed in warm benzene (200 ml.) on acid-washed alumina (21 × 3 cm.). Two bands and a mixed interband showing blue fluorescence in ultra-violet light were eluted with benzene (at *ca.* 40—50°

for the second band). On recovery, the second band gave **4 : 6-dimethoxycoumaranone** (3·2 g.), m. p. 134—138° alone or mixed with an authentic specimen. The first band gave **4 : 6-*dimethoxy*-5-*methylcoumaranone*** (1·8 g.) which was washed with light petroleum and crystallised from dilute ethanol (charcoal) in colourless needles, m. p. 146—147° [Found : C, 63·3, 63·7; H, 6·0, 6·1; OMe, 27·6; *C*-Me, 6·6%; *M* (Rast), 197. $C_{11}H_{12}O_4$ requires C, 63·45; H, 5·8; 2OMe, 29·8; 1*C*-Me, 7·2%; *M*, 208]. Absorption in EtOH : Max. at 327, 277, ~235 mμ (log ε 3·80, 4·20, ~3·97). The infra-red spectrum showed the presence of a carbonyl group absorbing at 1689 cm.$^{-1}$ but no semicarbazone, phenylhydrazone, or *p*-nitrophenylhydrazone could be prepared. The **2 : 4-*dinitrophenylhydrazone*** formed red needles (from nitrobenzene), m. p. 237—239° (Found : C, 52·4; H, 3·75; N, 14·4. $C_{17}H_{16}O_7N_4$ requires C, 52·6; H, 4·2; N, 14·4%).

Saturation of a mixture of the ketone (200 mg.) and benzaldehyde (100 mg.) in acetic acid (7 ml.) with hydrogen chloride at 10° caused separation of a complex from which the ***benzylidene*** derivative (175 mg.) was obtained by washing with water. It crystallised from ethanol in pale yellow needles, m. p. 175—175·5° (Found : C, 73·0; H, 5·3. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%).

A solution of the ketone (100 mg.) in 3N-sodium hydroxide (10 ml.) and methanol (10 ml.) was heated under reflux in nitrogen for 5 hr. The solid (90 mg.) which separated on cooling crystallised from light petroleum in colourless needles, m. p. 175—175·5°, of **2-(4 : 6-*dimethoxy*-5-*methyl*-3-*coumaronyl*)-4 : 6-*dimethoxy*-5-*methylcoumaran*-3-*one*** [Found : C, 66·3; H, 5·5; OMe, 31·1; *C*-Me, 7·3%; *M* (Rast), 438. $C_{22}H_{22}O_7$ requires C, 66·3; H, 5·6; 4OMe, 31·15; 2*C*-Me, 7·5%; *M*, 398). Absorption in EtOH : Max. at 324, 279, [254, 249], 234 mμ (log ε 3·73, 4·24, [4·10, 4·10], 4·31). The infra-red spectrum showed carbonyl absorption at 1700 cm.$^{-1}$ and absence of hydroxyl groups. The compound did not react with Brady's reagent and was unsaturated to neutral permanganate.

4 : 6-*Dimethoxy*-5-*methylcoumaranone*. (i) 4-Hydroxy-2 : 6-dimethoxytoluene (100 mg.) was converted by Horvath's procedure (*Monatsh.*, 1951, **82**, 901) into **ω-*chloro*-2-*hydroxy*-4 : 6-*dimethoxy*-5-*methylacetophenone*** (130 mg.), which crystallised from ethanol in needles, m. p. 114° (Found : C, 53·6; H, 5·6; Cl, 14·4. $C_{11}H_{13}O_4Cl$ requires C, 54·0; H, 5·4; Cl, 14·5%).

(ii) Ring closure of the above chloroacetophenone (130 mg.) in ethanol (20 ml.) with sodium acetate (200 mg.) in the usual way gave **4 : 6-dimethoxy-5-methylcoumaranone** (60 mg.), needles, m. p. 146—147° (from ethanol) (Found : C, 63·4; H, 5·8. Calc. for $C_{11}H_{12}O_4$: C, 63·45; H, 5·8%). The identity with material obtained from methylation of **4 : 6-dihydroxycoumaranone** was confirmed by mixed m. p., infra-red and ultra-violet absorption spectra, and formation of the same benzylidene derivative, m. p. and mixed m. p. 175° (Found : C, 73·2; H, 5·6. Calc. for $C_{18}H_{16}O_4$: C, 73·0; H, 5·4%).

4 : 6-*Dimethoxy*-7-*methylcoumaranone* was prepared from **2-hydroxy-4 : 6-dimethoxytoluene** by the method described above. The intermediate **ω-*chloro*-2-*hydroxy*-4 : 6-*dimethoxy*-3-*methylacetophenone*** (34% yield), pale yellow needles, had m. p. 184—184·5° (from ethanol) (Found : C, 53·9; H, 5·1; Cl, 13·9%). Although the compound did not react with Brady's reagent or give a colour with ferric chloride or titanous chloride (Weygand and Csendes, *Ber.*, 1952, **85**, 45), the infra-red absorption spectrum showed a strongly bonded hydroxyl band at 2670 cm.$^{-1}$ and carbonyl absorption with frequency lowered to 1630 cm.$^{-1}$. **4 : 6-*Dimethoxy*-7-*methylcoumaranone*** (59% yield) crystallised from ethanol in colourless needles, m. p. 177—178° (Found : C, 63·2; H, 5·9. $C_{11}H_{12}O_4$ requires C, 63·45; H, 5·8%). Absorption in EtOH : Max. at 320, 288, 234 mμ (log ε 3·50, 4·14, 3·95). The ***benzylidene*** derivative, obtained as described above, crystallised from ethanol in yellow needles, m. p. 244—245° (Found : C, 72·6; H, 5·3. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%).

The authors thank Dr. L. A. Duncanson for the infra-red absorption spectra, Dr. T. H. H. Quibell for a specimen, and Dr. F. Stansfield for details of an unpublished method of preparation, of 4-hydroxy-2 : 6-dimethoxytoluene.

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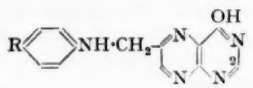
THE FRYTHE, WELWYN, HERTS. [*Received, January 14th*, 1953.]

335. *Some Pteridines related to Folic Acid. Part I. 2-Deamino-analogues.*

By D. J. Brown.

2-Deaminofolic acid {I; R = $CO{\cdot}NH{\cdot}CH{\cdot}CO_2H){\cdot}[CH_2]_2{\cdot}CO_2H$} and several related compounds having simpler side chains were prepared by condensing the appropriate primary amine with 6-bromomethyl-4-hydroxypteridine. The last-mentioned intermediate, and the corresponding 7-isomer, were prepared by direct bromination of 4-hydroxy-6(and 7)-methylpteridine by a procedure based on the successful ω-brominations of similar methylpteridines (Boothe *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 27; Waller *et al.*, *ibid.*, 1950, **72**, 4630; Tschesche, Köhncke, and Korte, *Z. Naturforsch.*, 1950, **5**, 132; *Chem. Ber.*, 1951, **84**, 485). The 6-bromo-compound in sodium hydroxide solution quickly gives an amorphous polymeric substance of unknown structure. The 7-isomer gives a similar substance more slowly.

The folic acid analogues were tested for folic acid activity. The determination of their metal-binding stability constants is described elsewhere (Albert, *Biochem. J.*, in the press).

(I) 

2-Deaminofolic acid, tested with *Strept. faecalis* R and *Lactobacillus casei* showed inhibitory, but no growth-promoting, activity. It was inactive as an inhibitor of the Walker rat carcinosarcoma 256, and, unlike xanthopterin, caused no hypertrophy of the rat kidney. It showed no capacity, as does " aminopterin," to arrest cell division in embryonic chick cells growing *in vitro*.

Experimental.—Analyses were by Mr. P. R. W. Baker, Beckenham. Each substance was purified until it showed only one spot on a paper chromatogram viewed in light of mainly 254 mμ.

6-*Bromomethyl*-4-*hydroxypteridine*. To a hot solution of 4-hydroxy-6-methylpteridine (18 g.; Albert, Brown, and Cheeseman, *J.*, 1952, 4219) in acetic acid (615 ml.) was added bromine (6·6 ml.) in acetic acid (60 ml.). The whole was refluxed until, about 8 min. later, boiling became more vigorous and the colour of the solution darkened rapidly. Immediately the flask was cooled in ice–water to about 45° and the solvent was removed in a vacuum at 40—45°. The dark green sticky residue was shaken with ice-cold water (35 ml.) for 10 min., and the solid which remained was filtered off and washed with water (20 ml.) and then with ethanol (3 × 20 ml.) (yield, 86%). When dried at 110° for 10 min. it became purple. Recrystallization from ethanol (80 parts) with charcoal (0·25 part) gave a 75—80% recovery of crystalline material suitable for further syntheses. Two more recrystallizations gave colourless needles of 6-*bromomethyl*-4-*hydroxypteridine quartohydrobromide*, decomp. >200° [Found: C, 32·3; H, 1·9; N, 21·4; Br, 37·8. $(C_7H_5ON_4Br)_3{\cdot}(C_7H_5ON_4Br,HBr)$ requires C, 32·2; H, 2·0; N, 21·4; Br, 38·2%]. It is unstable to cold alkali, all the bromine appearing as ion within 2 min. The aqueous solution is strongly acid.

7-*Bromomethyl*-4-*hydroxypteridine*. 4-Hydroxy-7-methylpteridine (Albert *et al.*, *loc. cit.*) was brominated in the same way (yield, 76%) but the reaction mixture was cooled at once after the addition of bromine. It was recrystallized twice from ethanol (150 parts) with carbon, to give colourless leaflets of 7-*bromomethyl*-4-*hydroxypteridine* (65% recovery), decomp. >170° (Found: N, 23·45; Br, 32·9. $C_7H_5ON_4Br$ requires N, 23·25; Br, 33·1%). This compound was but little changed by cold alkali after 5 min. Complete liberation of bromine as ion required 2 hr.' heating in water at 100° (pH <1 after a few min.).

6-*Anilinomethyl*-4-*hydroxypteridine* (I; R = H). 6-Bromomethyl-4-hydroxypteridine quartohydrobromide (2·3 g.), dissolved in boiling ethanol (180 ml.), was refluxed with aniline (2·5 ml.) for 2 hr. After refrigeration the crystalline product was filtered off, washed with ethanol, dried (yield, 67%), dissolved in sodium hydroxide solution (1%; 33 ml.), and reprecipitated by hydrochloric acid (pH 3—4). Recrystallization from 75 ml. of 6 : 4 amyl alcohol–dimethylformamide gave deep yellow crystals of 6-*anilinomethyl*-4-*hydroxypteridine*, decomp.

$>250°$ (Found: C, 62·2; H, 4·5; N, 27·4. $C_{13}H_{11}ON_5$ requires C, 61·65; H, 4·4; N, 27·65%), soluble in about 4000 parts of boiling water.

6-p-*Anisidinomethyl- and* 6-(2 : 5-*dimethoxyanilinomethyl*)-4-*hydroxypteridine*. The bromo-compound reacted similarly with *p*-anisidine. The yield was 70%. One recrystallization from amyl alcohol (1000 ml.) gave deep orange needles of 6-p-*anisidinomethyl*-4-*hydroxypteridine*, decomp. 240—260° (Found: C, 59·2; H, 4·4; N, 25·0. $C_{14}H_{13}O_2N_5$ requires C, 59·3; H, 4·6; N, 24·7%), soluble in about 3500 parts of boiling water.

The crude greenish-yellow solid obtained from 2 : 5-dimethoxyaniline, when recrystallized twice from water (1200 parts; carbon), gave yellow needles (15%) of 6-(2 : 5-*dimethoxyanilinomethyl*)-4-*hydroxypteridine hemihydrate* (dried at 120°) [Found: C, 55·5; H, 5·0; N, 21·7. $(C_{15}H_{15}O_3N_5)_2,H_2O$ requires C, 55·9; H, 5·0; N, 21·7%], soluble in dimethylformamide and acetic acid.

6-p-*Carboxyanilinomethyl*-4-*hydroxypteridine* (R = CO_2H). The bromo-compound (1·9 g.) and *p*-aminobenzoic acid (2·8 g.) reacted similarly. The crude product was ground with water (30 ml.) containing sodium hydroxide added to pH 4. The dried material was dissolved in warm dimethylformamide (40 ml.), and warm water (12 ml.) was added. The solution was brought to the boil, treated with carbon, and allowed to crystallize (yield, 28%). Repetition gave yellow needles of 6-p-*carboxyanilinomethyl*-4-*hydroxypteridine*, decomp. *ca.* 300° (Found: C, 56·55; H, 3·7; N, 23·55. $C_{14}H_{11}O_3N_5$ requires N, 56·7; H, 3·7; N, 23·55%). It dissolved in 2-ethoxyethanol.

4-*Hydroxy*-6-p-*sulphoanilinomethylpteridine*. 6-Bromomethyl-4-hydroxypteridine quarto-hydrobromide (3 g.) in ethanol (270 ml.) was refluxed with finely ground sodium sulphanilate (4·5 g.) for 2 hr. After refrigeration (12 hr.) the greenish solid was filtered off and dissolved in sodium hydroxide solution (0·5%; 100 ml.), and 2N-hydrochloric acid added to pH 2—3. After 1 hr. at 0°, the yellow crystals were filtered off (yield, 33%). Recrystallization from water (50 parts; carbon) gave yellow needles (75% recovery) of the *sodium* salt of 4-hydroxy-6-*p*-sulphoanilinomethylpteridine dihydrate, best dried in a vacuum (P_2O_5) at 20° (prolonged boiling in water caused decomposition) (Found: C, 17·8; S, 8·1. $C_{13}H_{10}O_4N_5SNa,2H_2O$ requires N, 17·9; S, 8·2%), soluble in about 200 parts of water at 20°.

2-*Deaminofolic acid*. To a solution of *p*-aminobenzoylglutamic acid (4 g.) (Tschesche *et al.*, *loc. cit.*, 1951) in ethanol (200 ml.) and aqueous potassium hydroxide solution (0·8N; 14·4 ml.) at 50—60° was added finely ground 6-bromomethyl-4-hydroxypteridine quartohydrobromide (3·2 g.). The mixture was at once placed under reflux in a boiling-water bath and vigorously shaken for 5 min. After 2 hr.' heating it was filtered hot and was refrigerated (after scratching if an oil was first deposited) for 24 hr. The solid was washed with alcohol (5 ml.) and dried in warm air (*ca.* 40°) and then for 5 min. at 110° (yield, 44%). It was twice recrystallized from preheated water (100 parts; carbon); rapid cooling of the filtrate gave, after refrigeration, 50% recovery. The light yellow crystalline 2-*deaminofolic acid* decomposed at ~170°. It was anhydrous after being dried at 90° in a vacuum, but hygroscopic (Found: C, 53·5; H, 4·2; N, 19·6. $C_{19}H_{18}O_6N_6$ requires C, 53·5; H, 4·25; N, 19·7%). It darkened slowly at 110° and the aqueous solution rapidly above *ca.* 80°. Small variations in the conditions led to loss of yield and quality of the product.

The author thanks Dr. R. H. Nimmo-Smith of the Microbiology Unit, Oxford, Professor A. Haddow of The Chester Beatty Research Institute, London, and Dr. W. Jacobson of the Strangeways Research Laboratory, Cambridge, who very kindly undertook the various biological tests.

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336. *Pyrimidine.*

By Norman Whittaker.

Pyrimidine was first obtained, and in 15—20% overall yield, by Gabriel and Colman (*Ber.*, 1899, **32**, 1525) from 6-methyluracil by a route involving reductive dechlorination of the 2 : 4-dichloro-6-methylpyrimidine with zinc dust and water to 4-methylpyrimidine. Gabriel (*Ber.*, 1900, **33**, 3666) similarly obtained pyrimidine directly by reducing **2 : 4** : 6-trichloropyrimidine, but **2 : 4 : 5** : 6-tetrachloropyrimidine (Emery, *Ber.*, 1901, **34**, 4180) gave a poor yield under the same conditions. More recently catalytic desulphurisation by Raney nickel of mercaptopyrimidines (Cavalieri and Bendich, *J. Amer. Chem. Soc.*, 1950, **72**, 2587; Boarland, McOmie, and Timms, *J.*, 1952, 4691) has been investigated, but with little success.

Magnesium oxide has been found useful in maintaining a neutral pH during the catalytic reductive dechlorination of simple chloropyrimidines by palladium catalysts and hydrogen (Whittaker, *J.*, 1951, 1565; see also Lythgoe and Rayner, *ibid.*, 1951, 2323; Boarland *et al.*, *loc. cit.*). By this means catalytic dechlorination of 2 : 4-dichloropyrimidine has now been effected on a half-molar scale with hydrogen under pressure, to give 75—80% yields of pyrimidine as a colourless hygroscopic solid, m. p. 22·5°, b. p. 124°/758 mm. This material was used for the spectrographic studies of a colleague, Dr. T. S. G. Jones, the results of which have been quoted by Boarland and McOmie (*J.*, 1952, 3716). Caustic alkali has no appreciable effect in the cold on pyrimidine (cf. Lythgoe and Rayner, *loc. cit.*) and is recommended for use in the isolation of pyrimidine from the reduction liquors to decompose the impurities present.

In an attempt to prepare 5-bromopyrimidine by the catalytic dechlorination of 5-bromo-2 : 4-dichloropyrimidine there was no break in the reduction curve until 3 mols. of hydrogen had been absorbed, and the product was again pyrimidine.

Experimental.—Pyrimidine. Pure magnesium oxide (freshly ignited; 50 g.) and palladium–charcoal (*ca.* 3% of Pd; 21 g.) were added to a suspension of 2 : 4-dichloropyrimidine (crystallised; 84 g.) in ethanol (420 ml.) and water (840 ml.), and the mixture agitated at room temperature under hydrogen at 30—40 lb. pressure. Absorption of hydrogen was complete after 80 min. The filtered liquid was distilled in steam and an excess of aqueous mercuric chloride added to the acidified distillate (pH 6) to give pyrimidine mercurichloride (172 g.). This was distilled with sodium sulphide (nonahydrate; 200 g.), and the aqueous distillate saturated with potassium hydroxide at 0—5°, solid pyrimidine separating. After warming to room temperature the upper pyrimidine layer was separated, and the lower aqueous layer (smelling strongly of ammonia) extracted with a little ether. The extract and the pyrimidine layer were combined, dried (KOH), and fractionated through a short packed column, to give pyrimidine (35 g., 78%), b. p. 123·5—124°/762 mm., m. p. 20·5—22·5°. The product was dissolved in water (50 ml.), treated with potassium hydroxide as described above, distilled over a little phosphoric oxide, and fractionally distilled, to give pure pyrimidine (31 g.), b. p. 124°/758 mm., m. p. 22·5°.

Pyrimidine methiodide (2·4 g.), m. p. 136—137°, separated from a solution of pyrimidine (1 g.) in methanol (2 ml.) containing methyl iodide (2 ml.) at room temperature. Recrystallised from ethanol it formed pale yellow plates of the same m. p. (Found: C, 27·0; H, 2·95; N, 13·2; I, 57·3. $C_5H_7N_2I$ requires C, 27·05; H, 3·15; N, 12·6; I, 57·2%).

5-Bromo-2 : 4-dichloropyrimidine. This was prepared by heating 5-bromouracil (10 g.), phosphoryl chloride (50 ml.), and diethylaniline (12 ml.) under reflux for 100 min. The product was isolated as described for 2 : 4-dichloro-5-nitropyrimidine (Whittaker, *loc. cit.*) as a colourless oil (10·5 g., 88%), b. p. 112—113°/12 mm., which solidified at room temperature (Found: N, 12·1; Ag halide, 211·4. Calc. for $C_4HN_2BrCl_2$: N, 12·3; Ag halide, 208·5%).

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337. *Cumyl Phenyl Ether.*

By A. M. Spivey.

During work on the separation of a mixture of phenol, αα-dimethylbenzyl alcohol, and acetophenone by fractional distillation under reduced pressure it was observed that, after most of the phenol and all of the acetophenone had distilled, a higher-boiling residue remained. This residue was a single, neutral compound, degraded by boiling 48% hydrobromic acid to a mixture of phenol and α-methylstyrene, the latter presumably resulting from dehydration of the preformed αα-dimethylbenzyl alcohol. This fact and the microanalysis indicate that the compound is cumyl phenyl ether, resulting from the condensation of phenol and the carbinol. The ease of its formation in good yield suggests that this type of condensation might be common between phenols and tertiary aromatic alcohols.

Several unsuccessful attempts, other than the direct condensation of the two components, were made to synthesise the ether and it may well be that direct condensation is the only route to this type of compound. α-Chlorocumene (Hoffman, *J. Amer. Chem. Soc.*, 1929, **51**, 2546) was treated with sodium phenoxide in ethanol but gave only a mixture of α-methylstyrene and phenol. Powell and Adam's method (*J. Amer. Chem. Soc.*, 1920, **42**, 656) for preparing benzyl phenyl ether was then applied, and a mixture of α-chlorocumene, phenol, and potassium carbonate in acetone was boiled under reflux but only phenol, α-methylstyrene, and *p*-cumylphenol could be isolated. The other known method for preparing alkyl aryl ethers, *viz.*, the warming of dry diazobenzene sulphate with αα-dimethylbenzyl alcohol gave only α-methylstyrene, probably because the acid-catalysed dehydration of the carbinol proceeded faster and at a lower temperature than the reaction forming the ether. Finally cumyl phenyl ether was synthesised in 20% yield by heating under reflux at reduced pressure a mixture of phenol and the carbinol, and was identical with the first specimen isolated. The reason for this low yield, compared with the higher yield obtained in the larger experiment in the presence of acetophenone, was not investigated, but it was shown that there was no reaction when phenol and acetophenone were boiled under reflux under similar conditions.

When most of this work had been completed it was noticed that Zal'kind and Kurlina (*J. Gen. Chem., Russia*, 1950, **20**, 2158) had observed the condensation between benzyl alcohol and phenol in the presence of acidic condensing agents. These authors, however, also isolated appreciable amounts of dibenzyl ether, *o*- and *p*-hydroxyphenylmethanes, and *o*- and *p*-benzylbenzyl alcohols as well as benzyl phenyl ether.

Experimental.—A mixture of phenol (125 g.), αα-dimethylbenzyl alcohol (50 g.), and acetophenone (25 g.) was fractionally distilled at 20 mm. through a column (122 × 2·3 cm.) packed with 4-mm. glass Fenske helices. At first pure phenol distilled but later fractions contained increasing amounts of acetophenone with traces of the carbinol and the last fraction to be collected contained a small amount of α-methylstyrene. At this stage, when 68% of the phenol and all the acetophenone (determined by infra-red analysis) had distilled, difficulty was experienced in maintaining the reflux, and distillation was therefore stopped. The residue crystallised to an almost colourless solid (35·4 g.), m. p. 46·5—48°; the total yield, including material recovered from the column, was 51 g. (66% on the carbinol). *Cumyl phenyl ether* formed needles (from ethanol), m. p. 47—48° (Found: C, 84·6; H, 7·5. $C_{15}H_{16}O$ requires C, 84·9; H, 7·6%) It was insoluble in aqueous acids and alkalis and soluble in most organic solvents.

Action of 48% hydrobromic acid on the ether. The ether (2 g.) was boiled under reflux with 48% hydrobromic acid (50 c.c.) for 2 hr., the mixture was diluted with water and extracted thrice with ether, and the combined ethereal extracts were extracted twice with 10% aqueous sodium hydroxide. The remaining ether solution was dried ($CaCl_2$) and concentrated to yield a mixture (0·75 g.) of the two dimers of α-methylstyrene, 4-methyl-2 : 4-diphenylpent-2-ene and 1 : 1 : 3-trimethyl-3-phenylindane (infra-red analysis), the unsaturated dimer predominating. The alkaline extract was acidified and extracted thrice with ether. The ethereal extract was dried (Na_2SO_4) and evaporated yielding a phenol whose 3 : 5-dinitrobenzoate (needles; m. p. 143·5—144·5°) did not depress the m. p. of an authentic specimen of phenyl 3 : 5-dinitrobenzoate.

Direct preparation of cumyl phenyl ether. A mixture of phenol (4·7 g.) and αα-dimethylbenzyl alcohol (6·8 g.) was boiled under reflux at 80 mm. for 12 hr. The mixture was distilled through a 6″ Vigreux column, and the fraction (6 g.), b. p. 80—85°/13 mm. consisting of phenol and α-methylstyrene, collected. The residue (2·0 g.; 20%) was recrystallised from ethanol giving the ether as needles, m. p. 47°, identical with the first specimen obtained from the mixture of phenol, the alcohol, and acetophenone.

The author is indebted to Mr. J. C. Hawkes for carrying out the infra-red analyses described and to the Directors for permission to publish this work.

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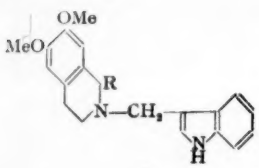
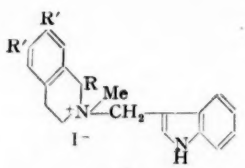
338. *Synthesis of* 1-*Alkyl*-1 : 2 : 3 : 4-*tetrahydro*-2-3′-*indolylmethyl*-6 : 7-*dimethoxy*isoquinolines *and the Ready Cleavage of their Methiodides.*

By J. M. OSBOND.

TOXIFERINE I has been shown to be the most potent curarising agent known (cf. Paton and Perry, *Brit. J. Pharmacol.*, 1951, **6**, 299). The complete structure of this alkaloid, which belongs to the calabash curare group, is not known, but it possesses a monoquaternary nitrogen in a tetrahydro*iso*quinoline ring, and a secondary non-basic nitrogen in an indole ring (Schmidt and Karrer, *Helv. Chim. Acta*, 1947, **30**, 1162). On this basis Craig and Tarbell (*J. Amer. Chem. Soc.*, 1949, **71**, 462) prepared 1 : 2 : 3 : 4-tetrahydro-2-3′-indolylmethyl*iso*quinoline methiodide (II; R = R′ = H) as a possible analogue (cf., however, Schmidt, Ebnother, and Karrer, *ibid.*, 1950, **33**, 1486), but this had only minimal activity. With a view to obtain a compound of greater activity the iodide (II; R = Et, R′ = OMe) has been synthesised in the hope that inclusion of two methoxy-groups in the tetrahydro*iso*quinoline moiety would enhance activity as in the bistetrahydro*iso*quinolylalkane dimethiodide series (cf. Craig, *Chem. Reviews*, 1949, **42**, 285; Taylor, *J.*, 1951, 1150).



(I)



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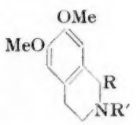

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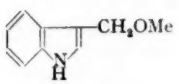

(IV)

1-Ethyl-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy*iso*quinoline (III; R = Et, R′ = H), prepared by catalytic reduction of the corresponding dihydro*iso*quinoline (cf. Dey and Govindachari, *Arch Pharm.*, 1939, **277**, 177), with indole and formaldehyde in aqueous acetic acid (cf. Kuhn and Stein, *Ber.*, 1937, **70**, 567) gave 1-ethyl-1 : 2 : 3 : 4-tetrahydro-2-3′-indolylmethyl-6 : 7-dimethoxy*iso*quinoline (I; R = Et). Treatment of this with excess of methyl iodide in benzene at room temperature gave a yellow oil which solidified. Considerable care had to be exercised in crystallising this methiodide (II; R′ = OMe, R = Et) for, although it was readily obtained pure by dissolution in cold methanol, from which it separated as small needles, in boiling methanol it gave the hydriodide of 1-ethyl-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-2-methyl*iso*quinoline (III; R = Et, R′ = Me). Cleavage of the Mannich base methiodide occurred even when a methanolic solution of the methiodide was set aside overnight at room temperature. From the methanolic mother-liquors the other fission product, 3-methoxymethylindole (IV), was obtained.

The instability of quaternary salts of 3-indolylmethylamines in alkaline medium is well known (Madinaveitia, *J.*, 1937, 1927; Geissman and Armen, *J. Amer. Chem. Soc.*, 1952, **74**, 3916) and is utilised in the tryptophan synthesis (cf. Snyder and Smith, *ibid.*, 1944, **66**,

350; Snyder and Eliel, *ibid.*, 1948, **70**, 3855) but cleavage does not appear to take place in neutral solution (cf. Snyder and Eliel, *ibid.*, 1948, **70**, 1703; Snyder, Thompson and Hinman, *ibid.*, 1952, **74**, 2009; Craig and Tarbell, *loc. cit.*; Geissman and Armen, *loc. cit.*). The instability of the methiodide (II; R′ = OMe, R = Et) in *neutral* conditions may possibly be due to the two methoxy-groups or the bulky ethyl group. We therefore treated 1 : 2 : 3 : 4-tetrahydro-2-3′-indolylmethyl-6 : 7-dimethoxy-1-methyl*iso*quinoline (I; R = Me) (Osbond, *J.*, 1951, 3464) in a similar way with methyl iodide in benzene at room temperature; the methiodide could not be obtained crystalline, but when in warm methanol it gave the hydriodide of 1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1 : 2-dimethyl*iso*quinoline (III; R = R′ = Me).

Dr. W. D. M. Paton reports that (II; R = Et, R′ = OMe), when injected intravenously (3 mg./kg.) into a cat under chloralose anaesthesia, has ganglionic blocking action, being *ca.* one-tenth as active as hexamethonium, with a transient depressor effect on the blood pressure; it reduced the pressor response to 0·5 mg. of nicotine considerably. There was no neuromuscular blocking, atropine, or adrenolytic action in doses up to 3 mg./kg.

Experimental.—*1-Ethyl-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy*iso*quinoline hydrochloride.* 1-Ethyl-3 : 4-dihydro-6 : 7-dimethoxy*iso*quinoline (6·27 g.) (Spath and Polgar, *Monatsh.*, 1929, **51**, 190) was hydrogenated in methanol (200 c.c.) in the presence of platinum oxide at room temperature and atmospheric pressure. After overnight shaking the catalyst was filtered off and the filtrate was taken to dryness and treated with concentrated hydrochloric acid. The hydrochloride separated from ethanol as prisms (5·5 g.), m. p. 214—215° (Found: C, 60·7; H, 8·0; N, 5·6. Calc. for $C_{13}H_{19}O_2N$,HCl: C, 60·6; H, 7·8; N, 5·4%). Dey and Govindachari (*loc. cit.*) record m. p. 214°.

*1-Ethyl-1 : 2 : 3 : 4-tetrahydro-2-3′-indolylmethyl-6 : 7-dimethoxy*iso*quinoline.* 1-Ethyl-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy*iso*quinoline hydrochloride (2·57 g., 1 mol.) was dissolved in water and made alkaline with 2N-sodium hydroxide and the base was extracted with ether (2 × 25 c.c.), washed with water, and dried (K_2CO_3). After removal of the ether the base was dissolved in aqueous acetic acid (10 c.c.; 50%); indole (1·17 g., 1·1 mol.) and then aqueous formaldehyde (0·75 c.c.; 40%; 1 mol.) were added successively at room temperature. The solution became warm and cloudy at once and gradually some amorphous solid separated. After 36 hr. at room temperature the mixture was extracted with ether, the aqueous layer made strongly alkaline, and the basic material extracted twice with ether. The ether was removed and the clear reddish gum was dissolved in benzene and diluted with light petroleum (b. p. 40—60°) and scratched, whereupon a white solid (1·63 g.) gradually crystallised. Two recrystallisations from benzene–light petroleum (b. p. 40—60°) and finally from *iso*propyl alcohol afforded the *base* as colourless prisms (0·9 g.), m. p. 132—133° (Found: C, 75·2; H, 7·4; N, 7·9. $C_{22}H_{26}O_2N_2$ requires C, 75·4; H, 7·5; N, 8·0%).

*Preparation and decomposition of 1-ethyl-1 : 2 : 3 : 4-tetrahydro-2-3′-indolylmethyl-6 : 7-dimethoxy*iso*quinoline methiodide.* (*a*) 1-Ethyl-1 : 2 : 3 : 4-tetrahydro-2-3′-indolylmethyl-6 : 7-dimethoxy*iso*quinoline (0·24 g.) was dissolved in methyl iodide (1·5 c.c.) at room temperature and set aside. After a few min. an oil began to separate. After 2 hr. light petroleum (b. p. 40—60°) was added and the supernatant liquor was decanted. The residual gum was dissolved in methanol at room temperature, and light petroleum (b. p. 40—60°) was added; the yellow oil which separated solidified when scratched (m. p. 90—110°). The *methiodide* was dissolved in methanol at room temperature and, on scratching, small colourless needles separated, having m. p. 110° (Found, on specimen dried over KOH at 0°: C, 52·6; H, 6·4; N, 5·3; H_2O, 5·7. $C_{23}H_{29}O_2N_2I$,1·75H_2O requires C, 52·7; H, 6·1; N, 5·3; H_2O, 6·0. Found, in sample dried at 100° *in vacuo*: C, 55·5; H, 6·1; N, 5·9. $C_{23}H_{29}O_2N_2I$ requires C, 56·1; H, 5·9; N, 5·7%). (*b*) The crude reaction product as obtained above was dissolved in boiling methanol and diluted with ether from which *1-ethyl-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-2-methyl*isoquinoline hydriodide separated as clumps of prisms, m. p. 212—214° (Found: C, 46·0; H, 6·1; N, 4·1. $C_{14}H_{21}O_2N$,HI requires C, 46·3; H, 6·1; N, 3·85%). The methanol mother-liquor was taken to dryness and the residue was extracted three times with boiling ether. The ethereal extracts were combined, filtered, and taken to dryness. The yellow crystalline material, m. p. 85—90°, was recrystallised from light petroleum (b. p. 40—60°) twice, to afford 3-methoxymethylindole as pale yellow prisms, m. p. 95—96° (Found: C, 74·5; H, 7·0. Calc. for $C_{10}H_{11}ON$: C, 74·5; H, 6·9%). Madinaveitia (*loc. cit.*) gives m. p. 99—100°. Geissman and Armen (*loc. cit.*) give m. p. 98—99°.

When the methanol mother-liquor from (*a*) was kept at room temperature overnight, 1-ethyl-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-2-methyl*iso*quinoline hydriodide, m. p. 212—213°, separated.

Preparation and decomposition of 1-*ethyl*-1 : 2 : 3 : 4-*tetrahydro*-2-3′-*indolylmethyl*-6 : 7-*dimethoxy*iso*quinoline methiodide*. 1-Ethyl-1 : 2 : 3 : 4-tetrahydro-2-3′-indolylmethyl-6 : 7-dimethoxy*iso*quinoline (0·57 g.; Osbond, *loc. cit.*) was dissolved in methyl iodide (2 c.c.) and set aside at room temperature for 2 hr. Ether was added to the solution and the methiodide collected. When, however, it was recrystallised from boiling methanol, small white nodules of 1-*ethyl*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-2-*methyl*iso*quinoline hydriodide* (0·28 g.), m. p. 204—207°, were obtained. One further recrystallisation from methanol ether gave the pure hydriodide as colourless prisms, m. p. 207—210° (Found: C, 44·8; H, 5·8; N, 4·2. $C_{13}H_{19}O_2N$,HI requires C, 44·7; H, 5·8; N, 4·0%). The picrate, prepared from a solution of the hydriodide by the addition of aqueous sodium picrate, separated from alcohol as yellow needles, m. p. 210° (Found: C, 50·3; H, 4·65; N, 12·4. Calc. for $C_{13}H_{19}O_2N,C_6H_3O_7N_3$: C, 50·7; H, 4·9; N, 12·4%). Spath and Passl (*Ber.*, 1929, **62**, 1021) give m. p. 212—213°.

The author thanks Dr. W. D. M. Paton for the biological tests.

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OBITUARY NOTICE.

SIR ROBERT WALEY COHEN

1877—1952.

SIR ROBERT WALEY COHEN, who died on November 28th 1952, was a man of the type only too rare in British industry at the turn of the century. He combined scientific inclination and training with a keen business mind and an unusual ability for organisation.

He was born in 1877 in London and received his scientific education at Cambridge where, as a Scholar of Emmanuel College, he took the Natural Science Tripos. In 1901 he joined the then very small petroleum company—The " Shell " Transport & Trading Company—and was associated with it for more than fifty years, rising with the passing of the years to become a leading member of the group of companies known as the Royal-Dutch/Shell Group, of which the " Shell " Transport and Trading Company became one of the " parents." He rose very rapidly to take his place among the three or four men who laid the foundations of that company, which has since become one of the largest international companies. His scientific outlook soon made itself felt, for by 1904 he was employing both science and arts graduates for positions of responsibility.

In those early days of the petroleum industry, when the possibilities of using " petrol " or " gasoline " in the internal combustion engine were beginning to be appreciated, it was thought that petroleum, from whatever source, had roughly the same chemical composition, and that the lower the specific gravity the better it would generally behave in the engine. Sir Robert was not satisfied with these generalities and set about tackling the problem from two angles—the composition of the petrol and its efficiency in the engine.

On the chemical side he interested Humphrey Owen Jones, of Cambridge, in the chemical composition of a variety of petrols and, on the other side, collaborated with Mr. (now Sir) Harry Ricardo, who developed the variable compression engine. The resultant story is now too well-known to need repetition here, but it was clear at the end of these researches that the aromatic content of the petrol played a considerable part in increasing the highest useful compression ratio possible in the internal combustion engine, and if the criterion of specific gravity was to be used to specify a petrol, the higher specific gravity and not the lower must be looked for.

The collaboration with Sir Harry Ricardo continued for many years, not only in petrol engines but in diesel engines and, latterly, in development of the gas turbine. Unfortunately, the collaboration with H. O. Jones was cut short by the latter's untimely death as a result of a climbing accident. Sir Robert commemorated this collaboration by the establishment in 1912 of the H. O. Jones Readership in Physical Chemistry at Cambridge.

Immediately after the 1914—18 war he took a prominent part in promoting the collection of a large sum of money from the petroleum companies for building the new Physical Chemistry Laboratory at Cambridge.

All this time he was continually looking to the universities to supply the kind of staff which " Shell " needed; he was intimately concerned with the setting up of the Appointments Board at Cambridge, remaining a member of its committee for many years. His assistance to the universities was by no means theoretical; he brought to their councils practical advice on the needs of industry and was always ready to encourage the progress of education. His influence on the Boards of the many companies associated with the Royal Dutch/Shell Group was always brought to bear in helping any worthwhile educational cause; the many scholarships and the Chair of Chemical Engineering at Cambridge bear witness to this, the seeds of which were sown in the first decade of this century by Sir Robert himself.

As Manager, and later Managing Director or Director, he always exerted a great personal influence. His relations with the staff were personal, and to men returning to England from abroad he was always available for discussion of their problems. He had an intimate knowledge of their working lives, for he had travelled widely himself; indeed, no one who has enjoyed the privilege of these inspiring talks with Sir Robert would ever think of " big business " as being cold and impersonal. However, if the picture of Sir Robert which is emerging is that of a benign old gentleman wishing a youngster good luck as he leaves for abroad, nothing could be farther from the truth. Woe betide the young man who visited Sir Robert in the hope that

he would not be asked anything too difficult! It was essential to know your facts when you entered his office.

It was one of Sir Robert's firm beliefs that a man could best serve the community, his country, and the world by doing his own job to the best of his ability. He did not believe in straying from his work as a leader in the petroleum industry to take part in politics or other activities outside his sphere, but it was inevitable that a man of his outlook and ability should be asked to help on many public bodies and when, in 1928, he relinquished his part in the day-to-day management of the Royal Dutch and Shell Companies for the somewhat less arduous—but for him hardly less active—work on the Board of the main company, he did from then until his death take a lively interest in other affairs. It is significant that most of these activities were concerned with education. He was Vice-Chairman of the Governors of University College, London, on the governing body of Imperial College of Science & Technology, and, as has already been said, an active member of the committee of the Cambridge Appointments Board. In addition he took the keenest interest in Jewish activities and, among other positions, was Chairman of the Jewish Memorial Council.

He remained with the one company for over fifty years; and saw it and the industry to which it belongs grow from very small beginnings into an international organisation with, as he firmly believed, an enormous power for good internationally. At the end of his career it was his proud boast that he was the oldest member of its staff, but he was equally proud to know that a large percentage of that staff had also made their life in the Group. His beliefs were simple: industry had first of all to satisfy its customers, the great public; for this it must have a keen, able, and happy staff, given which the right materials would always be available for the customer, and the company's prosperity would naturally follow.

It is difficult for one who has known him well not to create the impression of a fabulous personality, for he did indeed combine ability, energy, knowledge, and personal charm to a remarkable degree.

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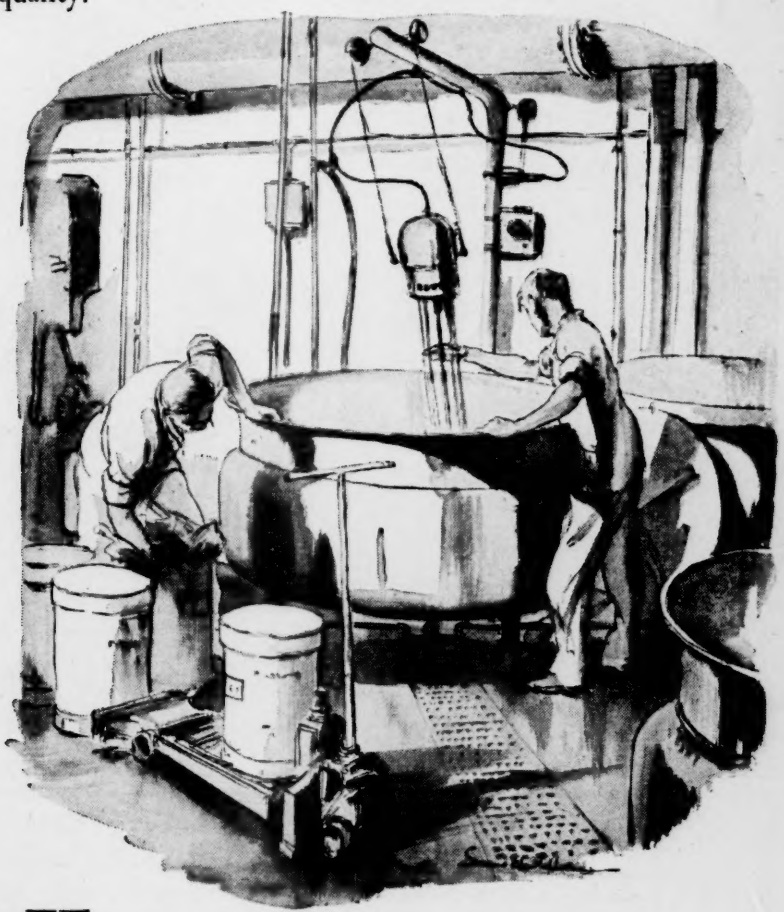

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